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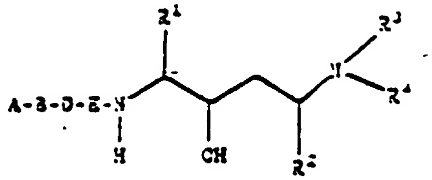
(54) Title of the Invention: New renin inhibitors, processes for production and their use in medications

The invention concerns new renin-inhibitory peptides of the general Formula I:



(I)

in which A, B, D, E, R^1, R^2, R^3 and R^4 have the meanings stated in the description, process for their production and their use in medications, particularly in medications affecting the circulation.

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The invention concerns new renin-inhibitory peptides, processes for their production and their application in medications, particularly in medications affecting the circulation.

Renin is a proteolytic enzyme produced predominantly by the kidneys and secreted into the plasma. It is known that in vivo renin splits the decapeptide angiotensin I from angiotensinogen. Angiotensin I is further degraded in the lungs, kidneys, or other tissues to the octapeptide angiotensin II, which elevates the blood pressure. The various effects of angiotensin II, such as vasoconstriction, Na^+ retention in the kidneys, aldosterone release in the adrenals, and increase of the tone of the sympathetic nervous system act synergistically, raising the blood pressure.

The activity of the renin-angiotensin system can be manipulated pharmacologically by inhibiting the activity of renin or of the angiotensin-converting enzyme (ACE), and by blocking angiotensin II receptors. Development of ACE inhibitors which can be administered orally has led to new antihypertensive agents (see German Laid-Open Patent 36 28 650, Am. J. Med. 77:690(1984)).

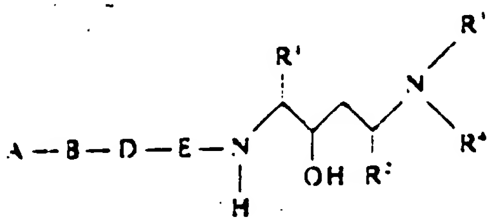
A more recent approach is to attack the renin-angiotensin cascade at an earlier point, that is, by inhibiting the highly specific protease, renin.

Various types of renin inhibitors have been developed so far: renin-specific antibodies, phospholipids, peptides with the N-terminal sequence of prorenin, synthetic peptides as substrate analogs, and modified peptides. In many renin inhibitors, also, the Leu/Val group is replaced by statin or by isosteric dipeptides (see European Patent Application 20 163 273).

The PCT WO 88/02374 also covers renin inhibitors which contain retro-isosteric dipeptide units as the protease-stable central portion. Retro-isosteric dipeptides have an amino group at the head end. Coupling to C-terminal amino acids leads to inversion of the amide function (retroamide).

New renin inhibitors have been found using the process according to the invention. They have surprisingly high selectivity for human renin, high stability to enzymatic degradation, and good oral efficacy.

The invention concerns peptides of the general Formula I:

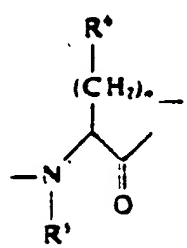


(I)

in which

A is hydrogen or C_1 - C_8 alkyl or C_1 -C_8 alkylcarbonyl or an amine-protecting group,

B is a direct linkage, or a group of the formula



(a)

in which

R^5 is hydrogen, C_1 - C_8 alkyl, phenyl, or an amine-protecting group,

n is the number 0, 1, 2, 3, or 4,

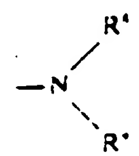
R^6 is hydrogen, C_1 - C_8 alkyl, hydroxymethyl, hydroxyethyl, carboxy, C_1 - C_8 alkylcarbonyl or mercaptomethyl or a group of the formula -CH_2-NH-R^7, wherein R^7 is hydrogen, C_1 - C_8 alkyl, phenylsulfonyl, C_1 - C_8 alkylsulfonyl or an amine-protecting group,

or

R^6 is phenyl, naphthyl, guanidinomethyl, methylthiomethyl, halogen, indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, possibly substituted by R^7,

in which R^7 has the meaning given above, or

R^7 is aryl which has up to three identical or different substituents of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1- C_3 alkylbenzyloxy, trifluoromethyl, halogen, hydroxy, nitro, or a group of the formula

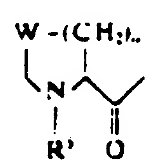


(b)

in which R^8 and R^9 are the same or different and are hydrogen, C_1 - C_8 alkyl, C_1 - C_6 alkylsulfonyl, aryl, arylalkyl, tolylsulfonyl, acetyl, benzoyl or an amine-protecting group,

or

B is a residue



(c)

in which

o is a number 1, 2, 3, or 4,

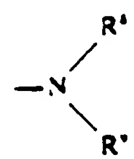
W is methylene, hydroxymethylene, ethylene or sulfur,

R^5 has the meaning given above;

D has the meaning given above for B, and may be the same as B or different,

E has the meaning given above for B, and may be the same as B or different,

R^1 is a straight or branched alkyl chain with 3 to 8 carbon atoms, which can be substituted with halogen, cyano, hydroxy, nitro, cycloalkyl with 3 to 8 carbon atoms, or phenyl, which itself can be substituted by C_1 - C_6 alkyl, nitro, cyano, or halogen, or aryl with 6 to 10 carbon atoms, which can have up to 4 identical or different substituents of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, phenyl, or a group



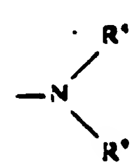
(d)

wherein R^8 and R^9 have the meanings stated above;

R^2 is hydrogen

or

a straight or branched alkyl chain with up to 10 carbon atoms, which may be substituted with halogen, hydroxy, cyano, nitro, or with a group



(e)

in which

R^8 and R^9 have the meanings stated above,

or by cycloalkyl with 3 to 8 carbon atoms,

or by phenyl which itself can be substituted by hydroxy, halogen, nitro, or C_1 - C_6 alkyl,

or is saturated or unsaturated cycloalkyl with 3 to 8 carbon atoms,

or is aryl with 6 to 10 carbon atoms, which may be substituted by halogen, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkoxyl, trifluoromethyl, trifluoromethoxy, C_1 - C_6 alkylsulfonyl or C_1 - C_6 alkylcarbonyl;

R^3 and R^4 are identical or different, and are hydrogen or

a straight or branched alkyl chain with up to 10 carbon atoms, which may be substituted by hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, cycloalkyl with up to 8 carbon atoms, heteroaryl or phenyl, which itself may be substituted by nitro, cyano, halogen, C_1 - C_6 alkyl,

or

cycloalkyl with 3 to 8 carbon atoms,

or

adamantyl

or

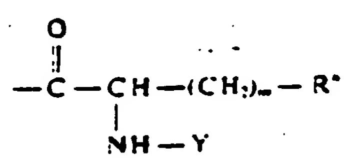
aryl with 6 to 10 carbon atoms, which may be substituted by hydroxy, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, carboxy, C_1 - C_6 alkylcarbonyl, phenyl, phenylsulfonyl, trifluoromethyl or trifluoromethoxy

or

formyl or C_1 - C_6 acyl

or

a group of the formula



(f)

wherein

m is a number 0, 1, 2, 4 [sic!] or 4,

R^6 has the meaning stated above,

and

Y is an amino-protecting group or a residue of the formula

$$-\overset{\overset{\displaystyle O}{\|}}{C}-R^{10} \qquad (g)$$

wherein

R^{10} is a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by aryl or heteroaryl,

and their physiologically acceptable salts.

As used in this invention, amino-protecting groups are the usual amino-protecting groups used in peptide chemistry.

They include, preferably:
benzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, dichlorobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, isopentoxycarbonyl, hexoxycarbonyl, cyclohexoxycarbonyl, octoxycarbonyl, 2-ethylhexoxycarbonyl, 2-iodohexoxycarbonyl, 2-bromoethoxycarbonyl, 2-chloroethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl,

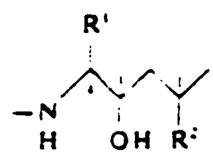
2,2,2-trichloro-tert-butoxycarbonyl, benzhydryloxycarbonyl, bis-(4-methoxyphenyl)methoxycarbonyl, phenacyloxycarbonyl, 2-trimethylsilylethoxycarbonyl, 2-(di-n-butyl-methylsilyl)ethoxycarbonyl, 2-triphenylsilylethoxycarbonyl, 2-(dimethyl-tert-butylsilyl)ethoxycarbonyl, menthyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, phenoxycarbonyl, tolyloxycarbonyl, 2,4-dinitrophenoxycarbonyl, 4-nitrophenoxycarbonyl, 2,4,5-trichlorophenoxycarbonyl, naphthyloxycarbonyl, fluorenyl-9-methoxycarbonyl, valeroyl, isovaleroyl, butyryl, ethylthiocarbonyl, methylthiocarbonyl, butylthiocarbonyl, tert-butylthiocarbonyl, phenylthiocarbonyl, benzylthiocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloroacetyl, 2-bromoacetyl, 2-iodoacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl, 4-nitrobenzyl, 4-nitrobenzoyl, naphthylcarbonyl, phenoxyacetyl, adamantylcarbonyl, dicyclohexylphosphoryl, diphenylphosphoryl, dibenzylphosphoryl, di-(4-nitrobenzyl)phosphoryl, phenoxyphenylphosphoryl, diethylphosphinyl, diphenylphosphinyl, phthaloyl, phthalimido or benzyloxymethylene.

Particularly preferred amino-protecting groups are:
benzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, cyclohexoxycarbonyl, hexoxycarbonyl, octoxycarbonyl, 2-bromoethoxycarbonyl, 2-chloroethoxycarbonyl, phenoxyacetyl, naphthylcarbonyl, adamantylcarbonyl, phthaloyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloro-tert-butoxycarbonyl, menthyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloroacetyl, 2-bromoacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, phthalimido or isovaleroyl or benzyloxymethylene.

The compounds of the general Formula I according to the invention contain several asymmetric hydrocarbons. They can occur in the D or L forms independently of each other. The invention includes the optical antipodes as well as the isomeric mixtures or racemates.

The groups B, D and E preferably occur in the optically pure form independently of each other, preferably in the L form.

The group of the formula



(h)

can, independently of the definition of the residue, have up to 3 asymmetric carbon atoms, which can occur independently of each other in the R or S configuration. Preferably, these groups occur in the 3S,4S configuration, the 3R,4S configuration if R^2 is hydrogen, in the 1R,3S,4S configuration, the 1R,3R,4S configuration, the 1S,3R,4S configuration, or in the 1S,3S,4S configuration, if R^2 is not hydrogen.

The 3S,4S configuration and the 1S,3S,4S configuration are especially preferred.

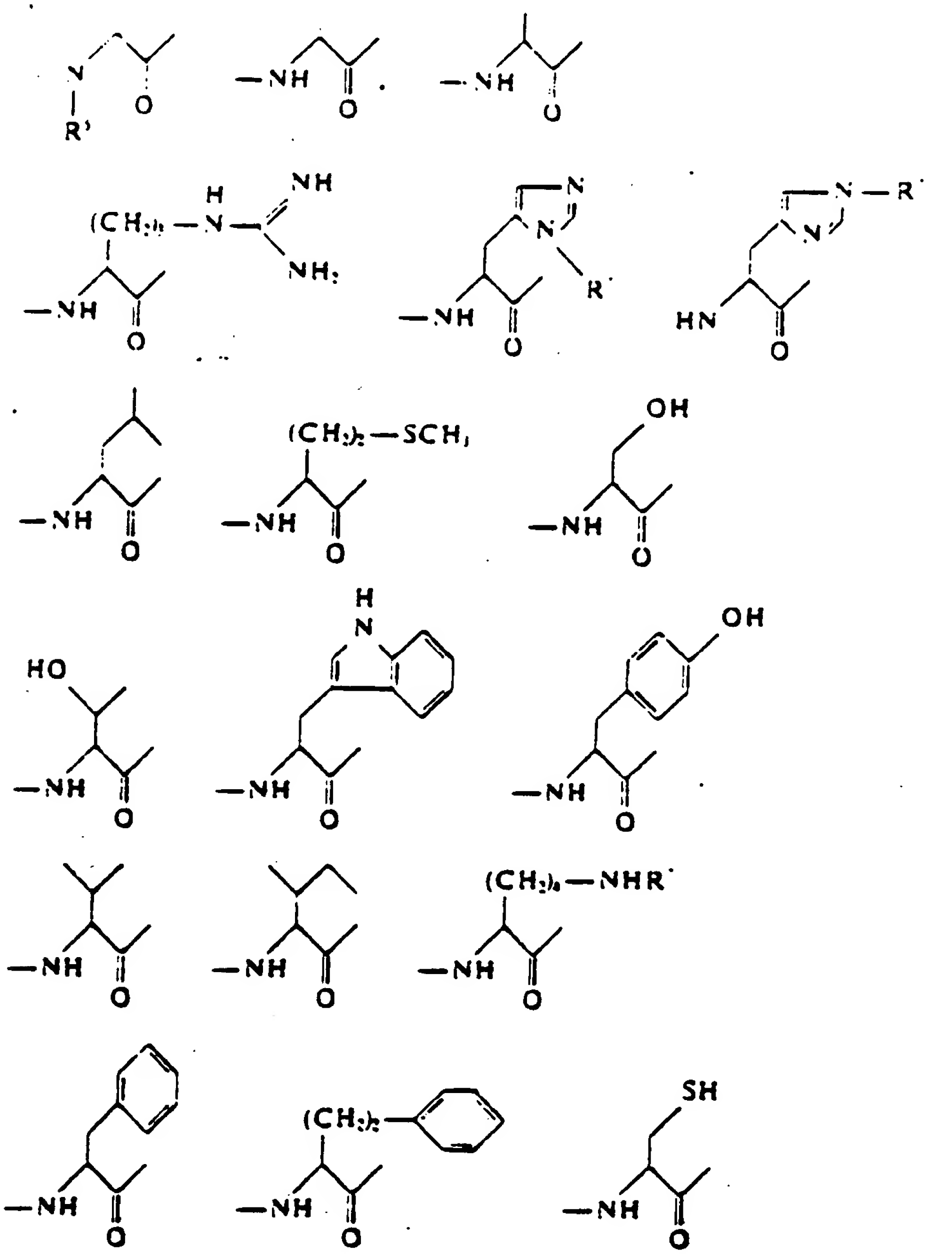
The compounds of the general Formula I according to the invention can occur as their salts. These can be salts of the compounds according to the invention with inorganic or organic acids or bases. The acid addition products include preferably salts with hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, or with carboxylic acids such as acetic acid, propionic acid, oxalic acid, glycolic acid, succinic acid, malic acid, hydroxymaleic acid, methylmaletic acid, fumaric acid, adipic acid, malic acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, lactic acid, ascorbic acid, salicylic acid, 2-ace-

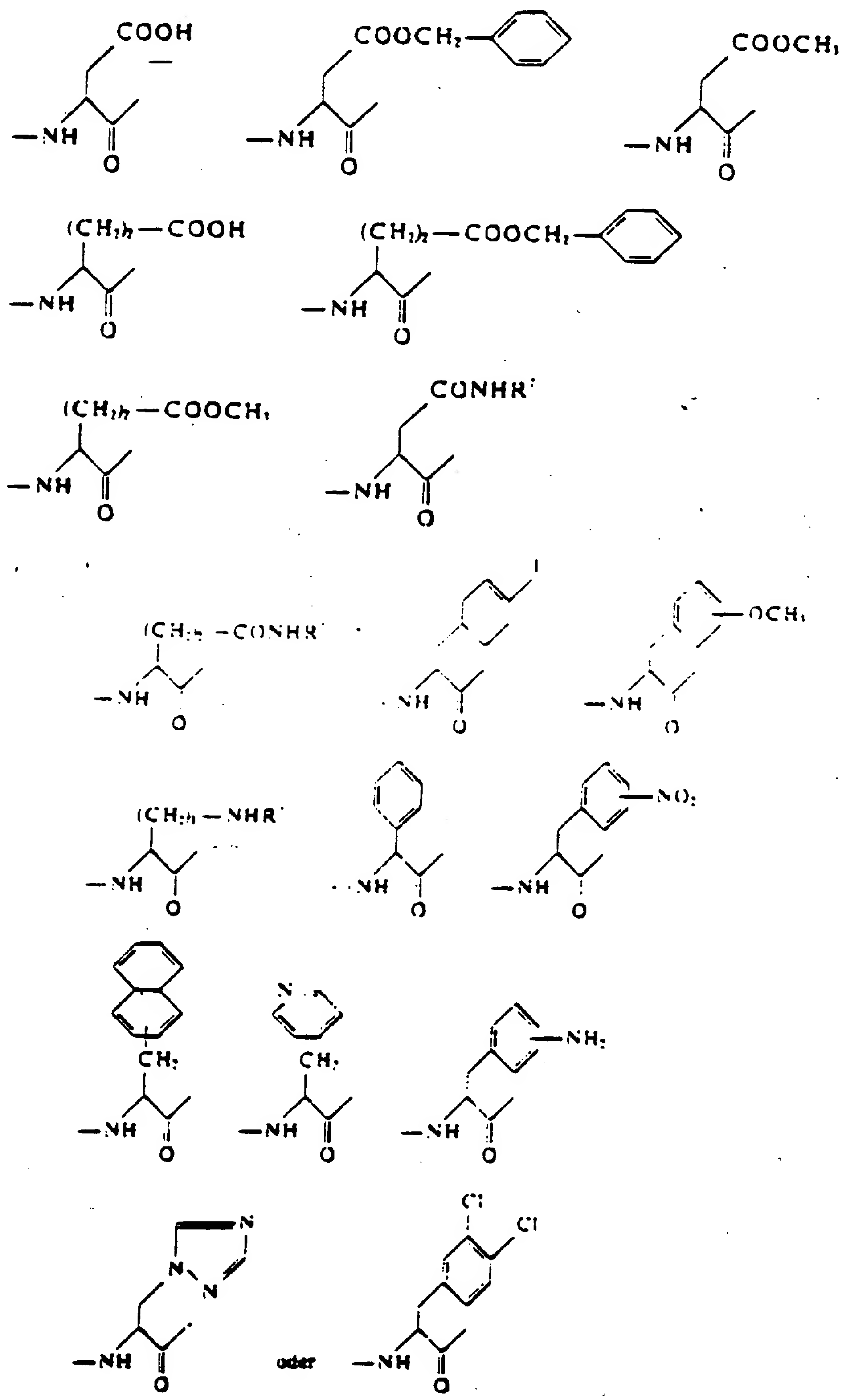
benzenesulfonic acid, toluene sulfonic acid, naphthalene-2-sulfonic acid or naphthalene disulfonic acids.

Preferred compounds of the general Formula (I) are those in which

A is hydrogen or C_1 - C_6 alkyl or C_1 - C_6 alkylcarbonyl or an amino-protecting group,

B is a direct linkage or a residue of the formula

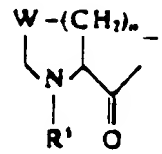




in their D form, L form, or as the DL isomeric mixture, preferably in the L form,

R^7 is hydrogen, C_1 - C_4 alkyl, phenylsulfonyl, C_1 - C_4 alkylsulfonyl, or an amine-protecting group,

B is a residue



(i)

wherein

R^5 is hydrogen, C_1 - C_6 alkyl, phenyl, or an amino-protecting group,

o is a number 1, 2, 3, or 4,

W is methylene

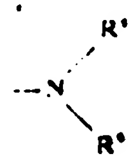
in its D form, L form, or DL isomeric mixture, and

D and E are identical or different, and have the same meaning as B, and are the same as B or different from B,

R^1 is a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by halogen, hydroxy, cycloalkyl with 3 to 6 carbon atoms, or phenyl,

or

is phenyl, which has up to 3 substituents of C_1 - C_3 alkyl, C_1 - C_3 alkoxy, hydroxy, nitro, or a group of the formula



(f)

wherein

R^8 and R^9 are identical or different, and are hydrogen, C_1 - C_4 alkyl, phenyl, or an amine-protecting group;

R^2 is hydrogen

or

a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by phenyl, which itself may be substituted by halogen, nitro, or C_1 - C_3 alkyl,

or

saturated or unsaturated cycloalkyl with 3 to 6 carbon atoms

or

phenyl, which may be substituted by halogen, nitro, C_1 - C_3 alkyl, C_1 - C_3 alkoxy or C_1 - C_3 alkoxycarbonyl

and R^3 and R^4 are identical or different, and are hydrogen

or

a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by hydroxy, nitro, thenyl, cycloalkyl with 3 - 6 carbon atoms or phenyl

or

adamantyl

or

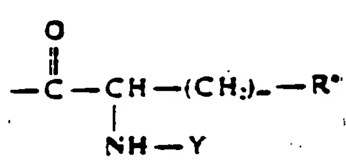
phenyl which may be substituted by hydroxy, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 alkoxcarbonyl

or

formyl

or

a group of the formula



(j)

wherein

m is a number 0, 1, 2, 3, or 4,

R^6 is hydrogen, C_1 - C_6 alkyl, hydroxymethyl, carboxy or a group $-CH_2-NH-R^7$, in which

R^7 is hydrogen, C_1 - C_6 alkyl, or an amine-protecting group;

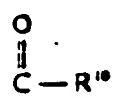
R^6 is guanidinomethyl, methylthiomethyl, halogen, indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, which may be substituted by R^7,

wherein

R_7 has the meaning given above,

or is phenyl, which may be substituted up to twice by halogen, hydroxy or nitro;

Y is an amine-protecting group or a residue of the formula



(1)

wherein

R^{10} is a straight or branched alkyl chain with up to 6 carbon atoms, which may be substituted by phenyl or heteroaryl,

and their physiologically acceptable salts.

Particularly preferred compounds of the general Formula (I) are those in which

A is hydrogen or C_1 - C_4 alkyl or C_1 - C_4 alkylcarbonyl or an amine-protecting group, preferably from the series benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, 2-bromoethoxycarbonyl, 2-chloroethoxycarbonyl,
2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, phenoxycarbonyl,

4-nitrophenoxycarbonyl, fluorenyl-S-methoxycarbonyl, acetyl, pivaloyl, phthaloyl, 2,2,2-trichloroacetyl, 2,2,2-trifluoroacetyl, benzoyl, 4-nitrobenzoyl, phthalimido, benzyloxymethylene, or tosyl;

b is a direct linkage or

glycyl (Gly), alanyl (Ala), arginyl (Arg), histidyl (His), leucyl (Leu), isoleucyl (Ile), seryl (Ser), threonyl (Thr), tryptophyl (Trp), tyrosyl (Tyr), valyl (Val), lysyl (Lys) (possibly with an amino-protecting group or with a methyl substituent on the nitrogen), phenylalanyl (Phe), 2- or 3-nitrophenylalanyl,

2-, 3-, or 4-aminophenylalanyl, naphthylalanine or pyridylalanyl (possibly with an amine-protecting group) in their L or D form,

or

D- or L-prolyl (Pro)

and

D and E are identical or different and have the same meaning as B, and may be the same as B or different;

R_1 is a straight or branched alkyl chain with up to 6 carbon atoms, which may be substituted by cyclopropyl, cyclopentyl or cyclohexyl;

R_2 is hydrogen

or

a straight or branched alkyl chain with up to 5 carbon atoms, possibly substituted by phenyl,

or

cyclohexenyl or cyclohexyl

or

phenyl, which may be substituted by fluorine, chlorine, nitro, methyl or methoxyl;

R^3 and R^4 are identical or different and

are hydrogen

or

a straight or branched alkyl chain with up to 6 carbon atoms, possibly substituted by thenyl, cyclopropyl, cyclopentyl, cyclohexyl or phenyl

or

adamantyl

or

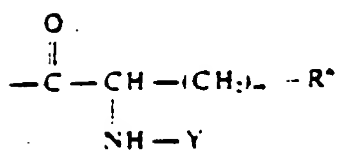
phenyl

or

formyl

or

a group of the formula



(m)

wherein

m is a number 0, 1, 2, or 3,

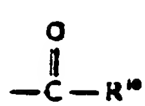
R^6 is hydrogen or C_1 - C_4 alkyl

and

Y is an amine-protecting group

or

a residue of the formula



(n)

in which

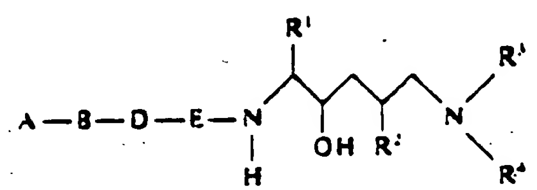
R^{10} is a straight or branched alkyl chain with up to 4 carbon atoms, possibly substituted by phenyl or pyridyl, and their physiologically acceptable salts.

Salts of the compounds according to the invention with salt-forming groups can be produced in ways which are themselves known, as by reaction of the compounds according to the invention which have acidic groups with corresponding bases, or by reaction of the compounds according to the invention which have basic groups with corresponding acids, always preferably with the acids and bases listed above.

Stereoisomeric mixtures, especially diastereoisomeric mixtures, can be separated into the individual isomers by known ways, such as by fractional crystallization or chromatography.

Racemates can be separated in known ways, such as by conversion of the optical antipodes into diastereoisomers.

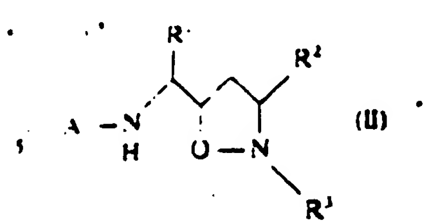
The inventions of the general Formula (I)



(o)

(I)

in which A, B, D, E, R^1, R^2, R^3 and R^4 have the meanings given above are obtained from compounds of the general Formula (II)



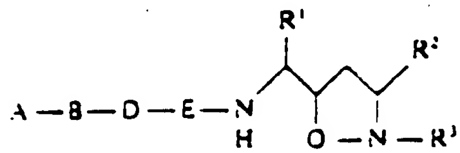
(p) (II)

in which A, R^1 and R^2 have the meanings stated above
either by

[A] first splitting off the protective group A and then in a second step reacting with compounds of the general Formula (III)

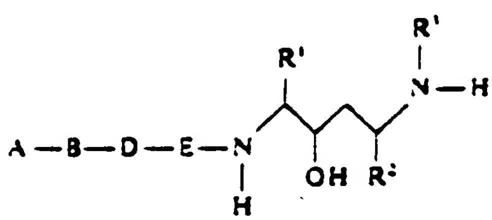
A-B-D-E-OH (III)

in which A, B, D, and E have the meanings stated above,
giving compounds of the general Formula (IV)



(q) (IV)

in which A, B, D, E, R^1 and R^2 have the meanings given above,
and then reducing to open the ring by hydrogenolysis, giving compounds of the general Formula Ia



(r) (Ia)

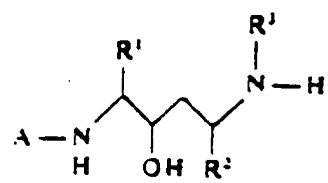
in which A, B, D, E, R^1 and R^2 have the meaning stated above,
and in the following step reacting with compounds of the general Formula (V)

$$R^4\text{-}OH \qquad (V)$$

in which R^4 has the meaning stated above;

or by

[B] first reducing compounds of the general Formula (II) to aminoalcohols of the general Formula (Ib)

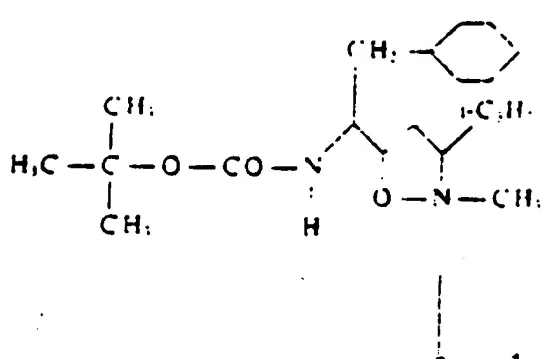


(Ib)

and then reacting with compounds of the general Formula (V), introducing the peptide fragment of the general Formula (III) by the method given above.

Depending on the nature of the starting compounds, the syntheses can be illustrated by the following example reaction scheme:

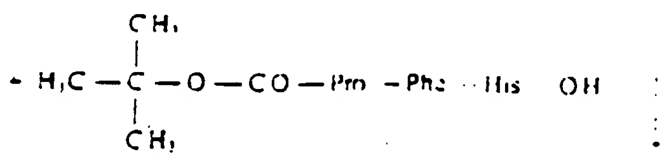
[A]



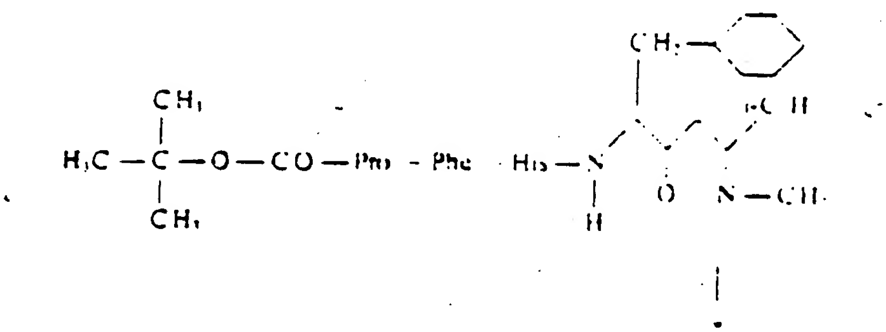
(t)

1. Splitting off the protective group

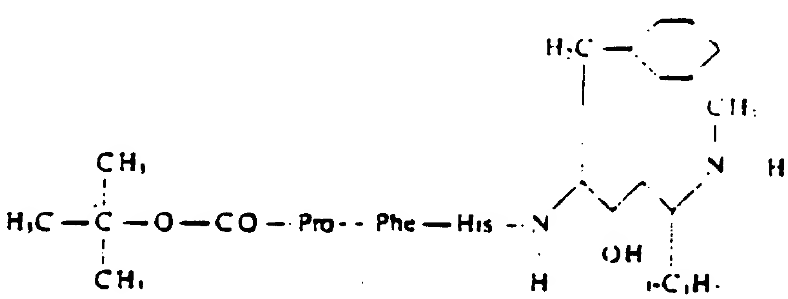
(u) 2. Coupling



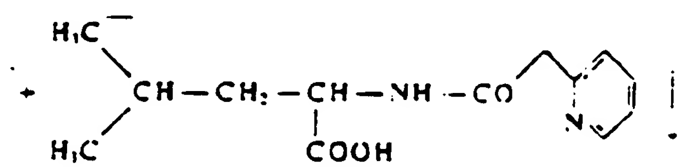
(v)



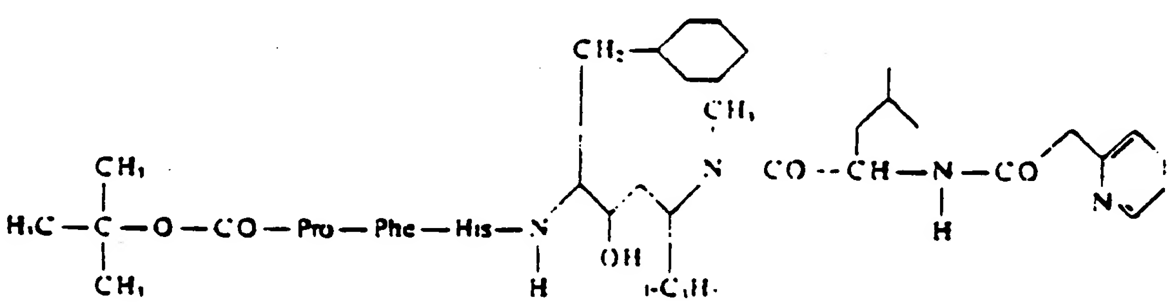
3. Reduction



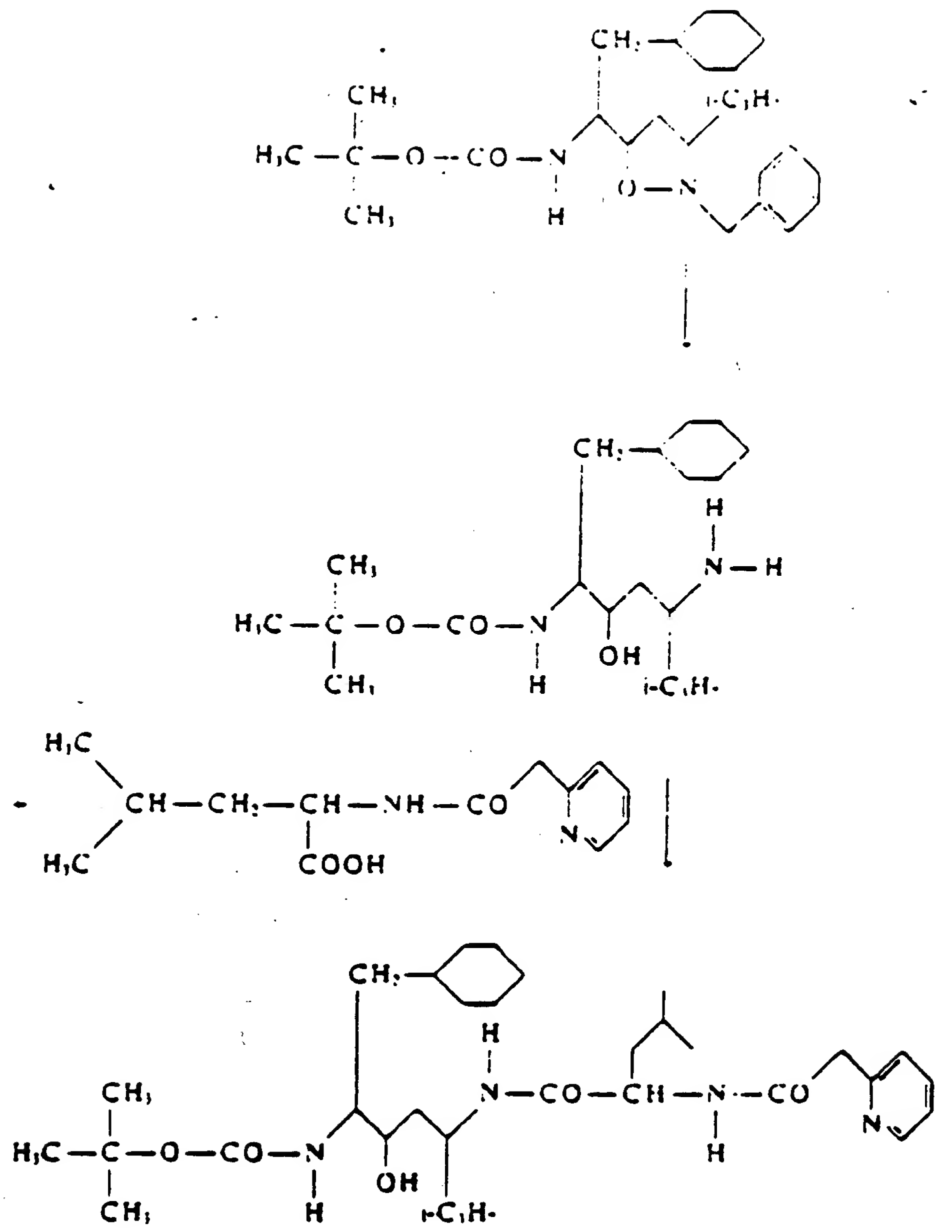
(w)



(x) 4. Acylation

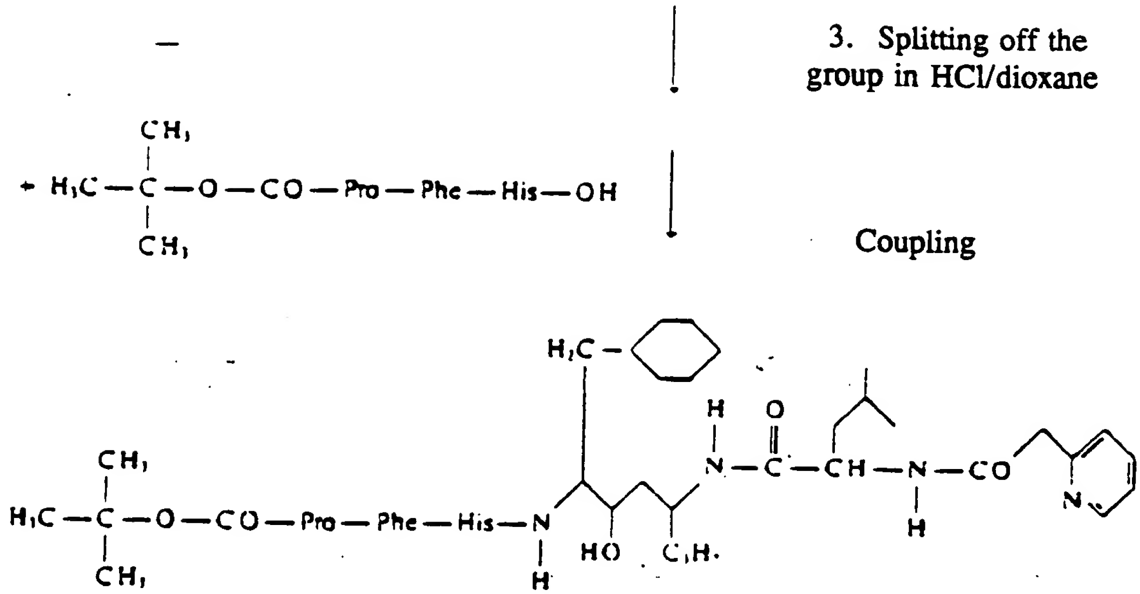


[B]



Reduction

2. Acylation


3. Splitting off the group in HCl/dioxane
Coupling

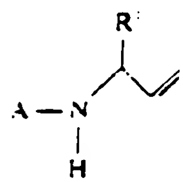
The usual inert solvents which do not change under the selected reaction conditions are suitable as solvents. These include preferably water or organic solvents such as methanol, ethanol, propanol, isopropanol or ethers such as diethyl ether, glycol mono- or di-methyl ether, dioxane or tetrahydrofuran, or hydrocarbons such as benzene, toluene, xylene, cyclohexane or petroleum fractions, or halogenated hydrocarbons such as methylene chloride, chloroform, or carbon tetrachloride, or acetone, dimethyl sulfoxide, dimethyl formamide, hexamethylphosphoric triamide, ethyl acetate, pyridine, trimethylamine or picoline. It is also possible to use mixtures of the solvents named. Dioxane is particularly preferred.

The process is usually carried out in the presence of suitable solvents or diluents, and if necessary, in the presence of an auxiliary substance or catalyst in a temperature range from -80°C to 300°C, preferably from -30°C to 200°C at normal pressure. It is also possible to work at elevated or reduced pressure.

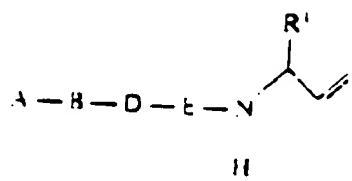
Condensing agents are preferably used as auxiliary materials. They can also be bases, especially if the carboxyl group is activated as the anhydride. The usual condensing agents preferred here are
carbodiimides such as N,N'-diethyl-, N,N'-dipropyl-, N,N'-diisopropyl-, and N,N'-dicyclohexyl-carbodiimide or
N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride,
or carbonyl compounds such as carbonyl-diimidazole,
or 1,2-oxazolium compounds such as
2-ethyl-5-phenyl-1,2-oxazolium-3-sulfonate or 2-tert-butyl-5-methyl-isoxazolium perchlorate,
or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline,
or propanephosphonic acid anhydride, or isobutyl chloroformate, or benzotriazolyloxy-tris-dimethylamino)phosphonium hexafluorophosphate,
or, as bases, alkali carbonates, e. g., sodium or potassium carbonate or bicarbonate,
or organic bases such as trialkylamines, e. g., triethylamine, N-ethylmorpholine or N-methylpiperidine.

The reduction can be accomplished in known ways,either with catalysts such as palladium hydroxide or palladium on carbon or by a catalytic transfer hydration (see Tetrahedron 41:3479(1985), 3463(1985), Synthesis 1987:53).

The compounds of the general Formulas (II) and (IV) are new, and can be produced by converting compounds of the general Formulas (VI) and (VII)

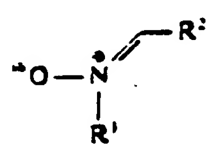


(VI)



(VII)

in which A, B, D, E and R^1 have the meanings stated
in a cycloaddition reaction with the compounds of the general Formula (VIII)



(VIII)

in which R^2 and R^3 have the meanings stated above.

-The usual organic solvents which do not change under the reaction conditions are suitable solvents. These include, preferably, alcohols such as methanol, ethanol, propanol, isopropanol, n-butanol, or ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol mono- or di-ethyl ether, or hydrocarbons such as benzene, toluene, xylene, or petroleum fractions, or n-butyl acetate. The preferred solvents are

n-butanol, dioxane, n-butyl acetate, toluene, xylene or mesitylene.

The reaction can be carried out in a temperature range from 0°C to 250°C , preferably at 100°C - 170°C and at normal or elevated pressure.

The compounds of the general Formula (VI) and (VII) are themselves known or can be produced by the usual methods [Chem. Pharm. Bull 30:1921(1982), Chem. Pharm. Bull. 23:3106(1976), J. Org. Chem. 47:3016(1982)].

The compounds of the general Formula (VIII) are themselves known or can be produced by the usual methods (J. J. Tufariello in: 1,3-Dipolar Cycloaddition Chemistry, Vol. 2, A. Padwa, Ed., pp. 83-168, John Wiley (1984); R. Huisgen, H. Seidel, J. Bruning, Chem. Ber. 102:1102(1969).

The compounds of the general Formula (III) can be produced by reaction an appropriate fragment consisting of one or more amino acid groups having a free carboxyl group, present in activated form if necessary, with a complementary fragment consisting of one or more amino acid groups having an amino group, present in activated form if necessary. This process is repeated with corresponding fragments until one had produced the desired peptide having the general Formula (III). Then the protective groups are split off, if necessary, or replaced by other protective groups.

Activated carboxyl groups preferred for this reaction are:
carboxylic acid azides (obtainable, for example, by reaction of protected or unprotected carboxylic acid hydrazides with nitrous acid, its salts, or alkyl nitrites (such as isoamyl nitrite),
or unsaturated esters, especially vinyl esters (obtainable, for example, by reacting an appropriate ester with vinyl acetate),
carbamoylvinyl esters (obtainable, for example, by reacting an appropriate acid with an isoxazolium reagent),

alkoxyvinyl esters (obtainable, for example, by reacting the corresponding acids with alkoxyacetylenes, preferably ethoxyacetylene)

or amidinoesters, such as N,N'- or N,N- disubstituted amidinoesters (obtainable, for example, by reaction of the corresponding acid with a N,N'-disubstituted carbodiimide (preferably dicyclohexylcarbodiimide), diisopropylcarbodiimide, or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) or with a N,N-disubstituted cyanamide

or aryl esters, especially phenyl esters substituted by electron-withdrawing substituents, such as 4-nitrophenyl, 4-methylsulfonylphenyl, 2,4,5-trichlorophenyl, 2,3,4,5,6-pentachlorophenyl, 4-phenyldiazophenyl esters (obtainable, for example, by reaction of the corresponding acid with an appropriately substituted phenol, if necessary in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, isobutyl chloroformate, or propanephosphonic acid anhydride)

benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate,

or cyanomethyl esters (obtainable, for example, by reacting the corresponding acid with chloroacetonitrile in the presence of a base),

or thioesters, especially nitrophenylthioesters (obtainable, for example, by reacting the appropriate acid with nitrothiophenols, if necessary in the presence of condensing agents such as N,N'-dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, isobutyl chloroformate, or propanephosphonic acid anhydride)

or benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate,

or amino- or amido-esters (obtainable, for example, by reaction of the appropriate acid with a N-hydroxylamino- or N-Hydroxylamido- compound, especially N-hydroxysuccinimide, N-hydroxypiperidine, N-hydroxyphthalimide, N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide or 1-hydroxybenzotriazole, if necessary in the presence of condensing agents such as N,N'-dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, isobutyl chloroformate, or propanephosphonic acid anhydride),

or anhydrides of acids, preferably symmetric or unsymmetric anhydrides of the corresponding acids, especially anhydrides with inorganic acids (obtainable, for example, by reaction of the corresponding acid with thionyl chloride, phosphorus pentoxide or oxalyl chloride)

or carboxylic acid hemi-derivatives such as carboxylic acid hemiesters with lower alcohols (obtainable, for example,by reaction of the corresponding acid with lower alkyl esters of chloroformic acid, such as methyl choroformate, ethyl chloroformate, propyl chloroformate, isopropyl chloroformate, butyl chloroformate or isobutyl chloroformate, or with 1-(lower-alkoxycarbonyl)-2-(lower-alkoxy)-1,2-dihydroquinoline, e. g., 1-methoxycarbonyl-2-ethoxy-1,2-dihydroquinoline)

or anhydrides of dihalophosphoric acids (obtainable, for example, by reaction of the corresponding acid with phosphorus oxychloride)

or anhydrides with phosphoric acid derivatives or phosphorous acid derivatives (e. g., propanephosphonic acid anhydride; H. Wissmann and H. J. Kleiner, Angew. Chem. Int. Ed. 19:133(1980))

or anhydrides with organic carboxylic acids (obtainable, for example, by reaction of the corresponding acids with a (possibly substituted) lower alkane or phenylalkane carboxylic acid halide, especially phenylacetic acid chloride, pivalic acid chloride, or trifluoroacetic acid chloride)

or anhydrides with organic sulfonic acids (obtainable, for example, by reaction of an alkali salt of a corresponding acid with a sulfonic acid halide, especially methanesulfonyl chloride, ethanesulfonyl chloride, benzenesulfonyl chloride or toluenesulfonyl chloride),

or symmetric anhydrides (obtainable, for example, by condensation of corresponding acids, if necessary in the presence of condensing agents such as N,N'-dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, isobutyl chloroformate, or propanephosphonic acid anhydride

or benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate.

Reactive cyclic amides are particularly amides with five-membered heterocycles having 2 nitrogen atoms and possibly aromatic character, preferably amides with imidazoles or

pyrazoles (obtainable, for example, by reaction of the corresponding acids with N,N'-carbonyldiimidazole or, if necessary in the presence of condensing agents such as N,N'-dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, isobutyl chloroformate, or propanephosphonic acid anhydride
or benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate,
with , for instance, 3,5-dimethylpyrazole, 1,2,4-triazole or tetrazole.

The amino acids used in definitions B, D and E are known, or can be obtained by known methods, or are naturally occurring amino acids (Houben-Weyl, "Methoden der organischen Chemie" [Methods of Organic Chemistry], Volumes XV, parts 1 and 2.

In vitro test

The inhibitory strength of the peptides according to the invention against endogenous renin from human plasma is determined in vitro. Pooled human plasma with ethylenediamine tetraacetic acid (EDTA) added as an anticoagulant is obtained and stored at -20°C. The plasma renin activity (PRA) was determined as the rate of formation of angiotensin I from endogenous angiotensinogen and renin after incubation at 37°C. The reaction solution contains 150 μl plasma, 3 μl 6.6% 8-hydroxyquinoline sulfate solution, 3 μl 10% dimercaprol solution and 144 μl sodium phosphate buffer (0.2 M; 0.1% EDTA; pH 5.6) with or without one of the substances according to the invention at various concentrations. The amount of angiotensin I formed per unit time is determined by radioimmunoassay (Sorin Biomedica, Italy). The percentage inhibition of the plasma renin activity is calculated by comparing the substances claimed here. The concentration range in which the substances claimed here show 50% inhibition of the plasma renin activity are between 10^{-4} and 10^{-9} M.

The new active substances can be made into the usual formulations, such as tablets, coated tablets, pills, granulations, aerosols, syrups, emulsions, suspensions and solutions in known ways, using inert nontoxic pharmaceutically suitable carriers or solvents. The therapeutically active compound should be present in a concentration from about 0.5% to 90% by weight of the total mixture; that is, in amounts that are sufficient to attain the specified dosage range.

The formulations are produced, for example, by diluting the active ingredients with solvents and/or carriers, if necessary with use of emulsifiers and/or dispersing agents. When water is used as the diluent, for instance, organic solvents may be used as auxiliary solvents if necessary.

Examples of auxiliary solvents are:
Water, non-toxic organic solvents such as paraffins (e. g., petroleum fractions), vegetable oils (e. g., peanut oil, sesame oil), alcohols (e. g., ethyl alcohol, glycerin), carriers, such as synthetic mineral flour (e. g., highly disperse silicic acid, silicates), sugar (e. g., sucrose, lactose and glucose), emulsifiers (e. g., polyoxyethylene fatty acid esters), polyoxyethylene fatty alcohol ethers (e. g., lignin, sulfite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e. g., magnesium stearate, talc, stearic acid and sodium sulfate).

Administration is accomplished in the usual manner, preferably orally or parenterally, especially perlingually or intravenously. In case of oral administration, tablets may obviously contain not only the carriers named but also additives such as sodium citrate, calcium carbonate and dicalcium phosphate along with various fillers such as starch, preferably potato starch, gelatin, and the like. Lubricants such as magnesium stearate, sodium lauryl sulfate and talc can also be included for tabletting. For aqueous suspensions, the active ingredients may be mixed not only with the auxiliary substances listed above but also with various dyes or substances to improve the flavor.

In case of parenteral administration, solutions of the active ingredients can be used with suitable liquid carriers.

In general, it has proved advantageous to administer amounts from about 0.01 to 10 mg/kg, preferably about 0.1 to 5 mg/kg body weight, to achieve effective results. In oral administration the dosage is about 0.1 to 200 mg/kg, preferably 0.1 to 100 mg/kg body weight.

Nevertheless, it may occasionally be necessary to depart from the amounts stated, depending on the body weight of the experimental animal or the mode of administration, and also depending on the animal species and their individual behaviors toward the medication, the nature of the formulations, and the time or time interval of administration.

In some cases, then, less than the lowest amount stated above may prove sufficient, while in other cases the upper limit stated must be exceeded. When larger amounts are administered it may be desirable to divide them into several separate doses through the day. The same dose range is planned for use in human medicine. Of course, the considerations presented above also apply here.

Appendix I

The following mobile phases were used:

A	Ether:hexane	2:8
B	Ether:hexane	3:7
C	Ether:hexane	4:6
D	Ether:hexane	7:3
E	CH_2Cl_2:CH_3OH	95:5
F	CH_2Cl_2:CH_3OH	98:2
G	CH_2Cl_2:CH_3OH	90:10
H	CH_2Cl_2:CH_3OH:NH_3	95:5:0.1
I	CH_2Cl_2:CH_3OH:NH_3	90:90:0.1
J	Tol:EE:CH_3OH	25:75:1
K	nBuOH:HOAc:H_2O	8:2:2
L	Tol:ethyl acetate	1:1

HPLC conditions: Vydac 218 TP 54, Vydac 218 TPB 10, (Bischoff 250 x 21.2 mm); Dynamax RP 18 (Rainin Instr., 250 x 21.4 mm), Brownlee Aquapore RP 300 10 μm (Kontron, 250 x 7 mm). Mobile Phase (A) 0.05% TFA/CH_3CN; (B) 0.05% TFA/H_2O. Flow rate, mixing ratio and gradients are reported. Detection at 214 nm.

Appendix II

Isomer	Configuration	
a	3S,4S	1R,3S,4S
b	3R,4S	1S,3S,4S
c	3R,4S	1S,3R,4S
d	3R,4S	1R,3R,4S

Appendix III

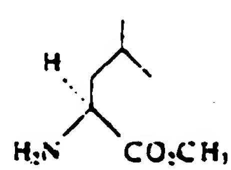
Abbreviations

AMP	2-aminomethylpyridine
BOC	t-butoxycarbonyl
BOM	Benzyloxymethylene
nPPA	n-propylphosphonic acid anhydride
Z	Benzyloxycarbonyl
PAA	Pyridylacetic acid

Starting Compounds and Example Preparations

Example 1

L-leucine methyl ester



(af)

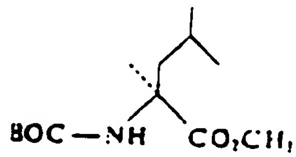
50 ml (0.685 mol) thionyl chloride is added, dropwise and with stirring, to 380 ml methanol at -5°C. Then 165 g (1.26 mol) L-leucine is added by portions (at 5°C). Then the mixture is slowly warmed to 40°C and stirred for 2 hours at that temperature.

The reaction solution is evaporated in a rotary evaporator and dried for about one hour at 100°C under vacuum. The residue is dissolved in about 150 ml H_2O, overlaid with 1500 ml diethyl ether, and adjusted to pH 9-10 with ammonia, with cooling.

The two phases are filtered off and separated. The ether phase is washed four times with 100 ml H_2O, dried over Na_2SO_4, and dried in a rotary evaporator.
Yield: 158 g ≙ 86.5% of theory.

Example 2

BOC-L-Leucine methyl ester



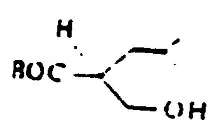
(ag)

158 g (1.09 mol) of the compound from Example 1 is dissolved in 180 ml (1.29 mol) triethylamine, 1200 ml dioxane, and 300 ml water, and stirred for 10 minutes. 315 g (1.44 mol) di-tert-butyl dicarbonate is added within a period of 30 minutes. Then the mixture is stirred for 5 hours at room temperature. The reaction mixture is next added to 2.5 liters of water. The pH is adjusted to 3 - 4 with citric acid and the solution is extracted three times with diethyl ether. The product is chromatographed on silica gel (mobile phase E) after drying over $MgSO_4$ and concentration.

Yield: 206.4 g (77.3%)

Example 3

BOC-Leucinol



(ah)

100 g (0.41 mol) of the compound from Example 2 is dissolved in 800 ml dry THF and added to a suspension of 32 g (0.84 mol) $NaBH_4$ and 110 g(0.82 mol) lithium iodide in

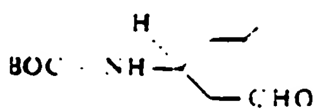
200 ml dry THF at 0°C. After reacting for 16 hours at 40°C, the reaction mixture is evaporated down. Ice water is added, and the mixture is adjusted to pH 2 with 1 N HCl. The pH is adjusted to 7 with solid $NaHCO_3$ and the mixture is extracted four times with methylene chloride. The organic phase is dried over Na_2SO_4 and evaporated.

Yield: 74.29 g (84.0%)

CI-MS: m/z = 218 (8% M [superscript illegible]), 162 (100%)

Example 4

BOC-Leucinal



(ai)

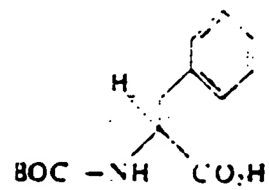
7.98 (36.8 mmol) of the compound from Example 3 is dissolved in 30.5 ml (220.8 mmol) triethylamine in anhydrous DMSO. With cooling by ice, 35.1 g (220.8 mmol) pyridinium sulfate is added, and the mixture is stirred for 15 minutes at 20°C.

Then the mixture is poured into ice water and extracted three times with ether. After washing with 2 M citric acid and saturated bicarbonate solution the solution is dried over $MgSO_4$. 6.32 g (79.8%) of a crude material is obtained. It is immediately processed further, or is stored for one to two days at -24°C.

NMR ($CdCl_3$, 250 MHz): δ = 9.65 (s: 1H, -CHO).

Example 5

BOC-Phenylalanine

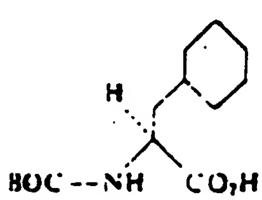


(aj)

300 g (1.91 mol) L-phenylalanine was suspended in 360 ml dioxane and 360 ml water. 432.9 g (1.98 mol) di-tert-butyl carbonate is added with stirring at pH 9.8. The pH is maintained constant with ca. 975 ml 4 N NaOH. After 16 hours the reaction mixture is extracted with ether. The aqueous phase is adjusted to pH 3-4 with citric acid and then extracted twice with ether and twice with ethyl acetate. The organic phases are combined and washed three times with water. After concentration in a rotary evaporator and crystallization from diethyl ether/hexane the yield is 291.6 g
(60.7%) mp 88-89°C
NMR(DMSO, 300 MHz): δ = 1.35 (s; 9H, $C(CH_3)_3$).

Example 6

BPC-cyclohexylalanine



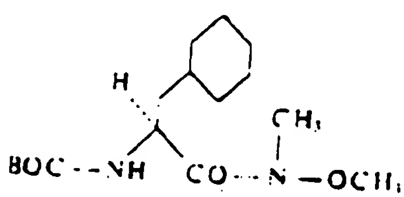
(ak)

265 g (1.0 mol) of the compound from Example 5 is dissolved in 2 liters of methanol and hydrogenated for 5 hours at 40 atm over 20 g of 5% Rh/C. The catalyst is filtered off by suction through Celite and washed with methanol. The solution obtained is evaporated. 271 g (100%) of Example 6 is obtained.

NMR (DMSO, 300 MHz): δ = 0.8 - 1.8 (m; 22H, cyclohexylmethylene, $C(CH_3)_3$)

Example 7

BOC-cyclohexylalanine-M-methyl-O-methyl hydroxamate



(al)

163.0 g (0.601 mol) of the compound from Example 6 and 40.3 g (0.661 mol) N,O-dimethylhydroxylamine are dissolved in 2 liters of methylene chloride at room temperature. 303.5 g (3.005 mol) triethylamine is added dropwise at 0°C.

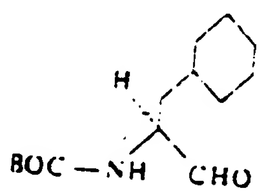
390.65 ml of a 50% solution of n-PPA in methylene chloride is added dropwise at not more than -10°C. The mixture is allowed to warm over-night to 25°C and stirred for 16 hours. Then the reaction solution is evaporated down. The residue is mixed with 500 ml saturated bicarbonate solution and stirred for 20 minutes at 25°C. After extracting three times with ethyl acetate the organic phase was dried over Na_2SO_4 and evaporated. Crude yield: 178 g (94.6%). The crude material was chromatographed on silica gel (mobile phase F).

Yield: 136.6 g (72.3%)

NMR (DMSO, 300 MHz): δ = 1.37 (s; 9H, $C(CH_3)_3$); 3.08 (s; 3H, N-CH_3);
3.71 (s; 3H; O-CHb3)

Example 8

BOC-cyclohexylalaninal



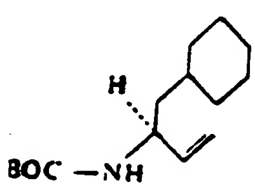
(am)

63.7 g (0.21 mol) of the compound from Example 7 is dissolved in 1.5 liters of aluminum oxide-treated ether under nitrogen in a baked-out apparatus. 10 g (0.263 mol) $LiAlH_4$ is added in portions at 0°C and the mixture is stirred for 20 minutes at 0°C. Then a solution of 50 g (0.637 mol) $KHSO_4$ in 1 liter H_2O is carefully added dropwise at 0°C. The phases are separated, and the aqueous phase is extracted three times with 300 ml diethyl ether. The combined organic phases are washed three times with HCl, 3 times with $NaHCO_3$ solution, and twice with NaCl solution. The organic phase is dried over Na_2SO_4 and evaporated. Yield: 45 g (884.1%). The aldehyde is either further processed immediately or stored for one to two days at -24°C.

NMR (DMSO, 300 MHz): δ = 9.41 (s; 1H, -CHO).

Example 9

BOC-allylalanine



(an)

14.6 g (35 mmol) "Instant Ylide" (Fluka 69500) is suspended in 90 ml anhydrous tetrahydrofuran. A solution of 9.0 g (35 mmol) BOC-cyclohexylalaninal in 45 ml anhydrous

tetrahydrofuran is added dropwise with cooling by ice at a reaction temperature between 20 and 25°C. After stirring for 15 minutes, the reaction mixture is poured onto 250 ml ice and extracted twice with 150 ml ethyl acetate/n-hexane 3:1. After drying over Na_2SO_4 and evaporation, the residue is chromatographed on silica gel (mobile phase D).

Yield: 3.2 g(40.0%)

EI-MS: m/z = 253 (0.1% M + H), 197 (9%)

Example 10

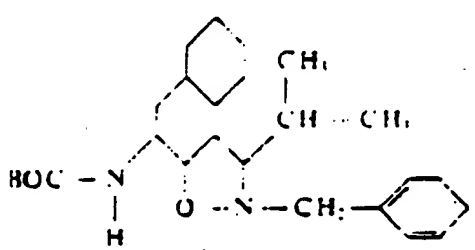
BOC-allylamine

The preparation is done as described in Example 9, using 0.24 mole.

Yield: 25.92 g (50.6%).

Example 11

Isoxazolidine



(ao)

3.8 g (15.0 mmol) of the compound from Example 9 is dissolved in 55 ml xylene and heated to 140°C on the water bath. A mixture of 8.3 g (67.5 mmol) N-benzylhydroxylamine and 6.1 ml (67.5 mmol) methylpropanol[1] in 45 ml xylene is added dropwise at that temperature over a period of 2 hours. The same amounts of N-benzylhydroxylamine and methylpropanal in xylene are added dropwise after 4 and 8 hours of reaction time. After a total reaction

[1] Translator's Note: The German text first speaks of methylpropanol and then of methylpropanal. They are different. The original text has been left unchanged.

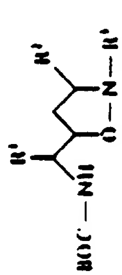
time of 16 hours the mixture is evaporated. The residue is mixed with ether and then washed with 1 M $KHSO_4$ solution. After drying over Na_2SO_4 and evaporation, the mixture is chromatographed on silica gel (mobile phase D).

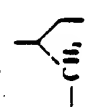
Yield: 5.163 g (80.0%)

The examples 12-26 presented in Table 1 were prepared analogously to the description for Example 11.

Translator's Note: Table 1 covers 4 pages in the original German text. Only the column headings need translation:

Beispiel Nr	=	**Example No.**
Ausbeute	=	**Yield**
Summenf.	=	**Empirical formula**
DC	=	**Thin-Layer Chromatography**
FAB-MS	:	**leave as is (Fast Atom Bombardment - Mass Spectrometry)**



Beispiel Nr	R¹	R²	R³	Ausbeute [%]	DC, RF	¹H-NMR C-4-NH	H-3	Summenf	FAB-MS M+H [%]
12 a	iC₄H₉	H	CH₃	83,2	0,27D	6,46	4,08	$C_{[illegible]}H_{[illegible]}N_2O_4$	272 [6] FI
b					0,18D	6,68	3,83		272 [3] FI
13 a	iC₄H₉	H	iC₃H₇	91,8	0,51E	6,41	3,83	$C_{[illegible]}H_{[illegible]}N_2O_4$	301 [100]
b					0,42E	6,62	3,65		301 [100]
14 a	iC₄H₉	H	 CH₂	48,5	0,49D	6,50	4,00	$C_{[illegible]}H_{[illegible]}N_2O_4S$	355 [100]
b					0,41D	6,70	3,85		355 [100]
15 a	iC₄H₉	H		48,3	0,41C	6,42	3,90	$C_{[illegible]}H_{[illegible]}N_2O_4$	329 [100]
b					0,26C	6,62	3,70		329 [100]
16 a	iC₄H₉	H	Adamantyl	5,0	0,18C	6,39	3,70	$C_{[illegible]}H_{[illegible]}N_2O_4$	393 [100]
b					0,09C	6,60	3,55		393 [100]
17 a	iC₄H₉	H		70,0	0,27B	6,45	3,83	$C_{[illegible]}H_{[illegible]}N_2O_4$	327 [100]
b					0,20B	6,45	3,78		327 [100]
c			CH₃		0,15B	6,63	3,66		327 [100]
d					0,11B	6,65	3,63		327 [100]

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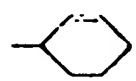
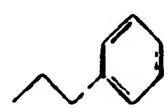
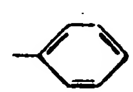
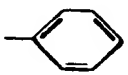
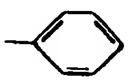
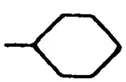
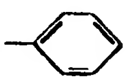
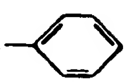
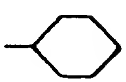
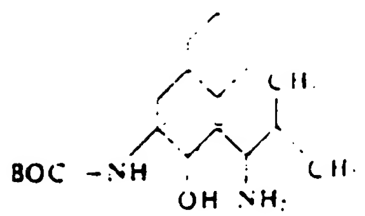
Beispiel Nr	R^1	R^2	R^3	Ausbeute [%]	DC, Rf	^{1}H-NMR C-4-NH	H-3	Summenformel	FAB-MS $M+H^+$
18 a	iC_4H_9	CH_3	CH_3	29,2	0,36C	6,31	3,96	$C_{15}H_{[illegible]}N_2O_{[illegible]}$	286 [11]
b					0,22C	6,53	3,72		
c					0,17C	6,39	3,80		
d					0,08C				
19 a	iC_4H_9	nC_3H_7	CH_3	56,9	0,51C	6,29	4,01	$C_{17}H_{[illegible]}N_4O_{[illegible]}$	315 [100]
b					0,39C	6,58			315 [100]
c					0,33C	6,43	3,78		315 [100]
d					0,25C	6,68	3,62		315 [100]
20 a	iC_4H_9	iC_3H_7	CH_3	31,3	0,44B	6,38	4,07	$C_{17}H_{[illegible]}N_4O_{[illegible]}$	315 [100]
b					0,34B	6,65	3,82		
c					0,34B	6,50	3,73		
d					0,29B	6,69	3,61		
21 a	iC_4H_9		CH_3	35,6	0,68C	6,35	3,95	$C_{20}H_{[illegible]}N_2O_{[illegible]}$	353 [100]
b					0,55C	6,48	3,55		353 [100]
c					0,51C	6,68	3,50		353 [100]
d							3,63		
22 a	iC_4H_9		CH_3	37,0	0,44C	6,40	4,07	$C_{22}H_{[illegible]}N_2O_{[illegible]}$	377 [100]
b					0,35C	6,63	3,82		377 [100]
c					0,30C	6,49	3,80		377 [100]
d					0,21C	6,68	3,69		377 [100]
23 a	iC_4H_9		CH_3	45,2	0,89E	6,31	4,13	$C_{20}H_{[illegible]}N_4O_{[illegible]}$	349 [100]
b					0,81E	6,58	4,02		349 [100]
c					0,81E	6,63	3,85		
d					0,70E	6,72	3,89		349 [100]

Beispiel Nr	R^1	R^2	R^3	Ausbeute [%]	DC, RF	^{1}H-NMR C-4-NH	H-3	Summenf.	FAB-MS M+H [%]
24 a	iC_4H_9	CH_3	CH_2— 	27,0	0,72C	6,39	4,02	$C_{20}H_{26}N_2O_4$	363 [98]
b					0,59C	6,60	3,64		363 [100]
c					0,46C	6,45	3,80		363 [98]
d					0,39C	6,67			363 [100]
25 a	iC_4H_9	iC_3H_7	CH_2— 	60,0	0,53A	6,42	4,17	$C_{22}H_{30}N_2O_4$	391 [36]
b					0,33A	6,47	(3,80)		391 [55]
c					0,29A	6,64	(3,85)		391 [·22]
d					0,23A	6,69	3,62		391 [33]
26 a	CH_2— 	iC_3H_7	CH_3	58,8	0,36B	6,31	4,05	$C_{19}H_{30}N_2O_4$	355 [100]
b					0,25B	6,60			
c					0,25B	6,42	3,75		355 [100]
d					0,17B	6,64	3,60		355 [100]

Beispiel Nr.	R^1	R^2	R^3	Ausbeute [%]	DC, Rf	^{1}H-NMR C-4-NH	H-3	Summenf.	FAB-MS M+H [%]
24 a	iC_4H_9	CH_3	CH_2— 	27,0	0,72C	6,39	4,02	C[illegible]H[illegible]N[illegible]O[illegible]	363 [98]
b					0,59C	6,60	3,64		363 [100]
c					0,46C	6,45	3,80		363 [98]
d					0,39C	6,67			363 [100]
25 a	iC_4H_9	iC_3H_7	CH_2— 	60,0	0,53A	6,42	4,17	C[illegible]H[illegible]N[illegible]O[illegible]	391 [36]
b					0,33A	6,47	(3,80)		391 [55]
c					0,29A	6,64	(3,85)		391 [22]
d					0,23A	6,69	3,62		391 [33]
26 a	CH_2— 	iC_3H_7	CH_3	58,8	0,36B	6,31	4,05	C[illegible]H[illegible]N[illegible]O[illegible]	355 [100]
b					0,25B	6,60			–
c					0,25B	6,42	3,75		355 [100]
d					0,17B	6,64	3,60		355 [100]

Example 27

BOC-aminoalcohol

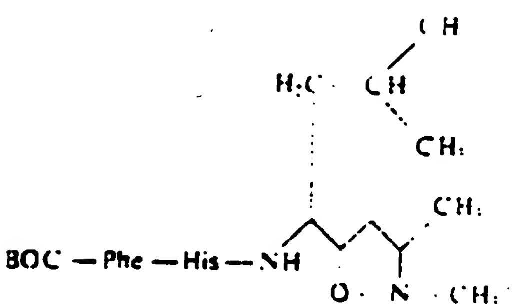


(ap)

500 mg (1.2 mmol) of the compound from Example 11 and 756 mg (12 mmol) are dissolved in 20.0 ml methanol. 100 mg Pd/C is added and the mixture boiled with reflux for 1 hour. The reaction solution is suction-filtered through silica gel and evaporated. The residue is dissolved in diethyl ether, extracted twice with $NaHCO_3$ solution and then evaporated. Yield: 476.8 mg (~ 100%).

Example 28

Peptidyl-isoxazolidine



(aq)

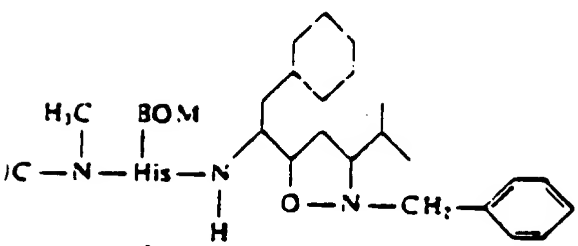
57.1 mg (0.2 mmol) of the compound of Example 18 is stirred in 1 ml 4 N HCl/dioxane with moisture excluded. After evaporation, the substance is repeatedly mixed with diethyl ether and evaporated down. The residue is dissolved in 10 ml methylene chloride with

124.7 mg (0.31 mmol) BOC-Phe-His-OH, 94.91 mg (0.62 mol) hydroxybenzotriazole and 0.034 ml (0.31 mmol) N-methylmorpholine. After cooling to 0°C, 67.1 mg (0.326 mol) dicyclohexylcarbodiimide is added and the mixture is stirred for 16 hours at 20°C. The reaction mixture is evaporated, dissolved in ethyl acetate, and washed with saturated $NaHCO_3$ solution and water. The organic phase is dried over Na_2SO_4, filtered, and evaporated.

Yield: 173.6 mg (98.1%).

Example 29

Peptidylisoxazolidine



(ar)

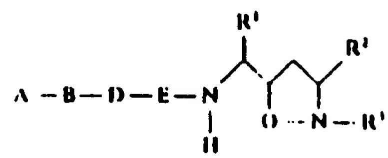
1.399 g (3.24 mmol) of the compound from Example 11 is deblocked with 16.2 ml 4 N HCl/dioxane and dried in high vacuum. 770 mg (2.1 mmol) of the hydrochloride is dissolved in 20 ml anhydrous tetrahydrofuran with 817 mg (2.1 mmol) BOC-N-methyl-His-(BOM)-OH, 568 mg (4.2 mmol) hydroxybenzotriazole and 0.23 ml (2.1 mmol) N-methylmorpholine. 476 mg (2.3 mmol) dicyclohexylcarbodiimide is added at 0°C and stirred for 16 hours at 20°C. After the urea is filtered off by suction, the filtrate is evaporated and the residue is dissolved in ethyl acetate. After washing the organic phase with saturated bicarbonate solution and drying it over Na_2SO_4, it is filtered and evaporated. The crude material, 1.1 g (74.7%) is chromatographed on silica gel (mobile phase E). 519.0 mg (37.0%) is obtained.

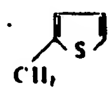
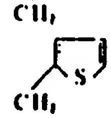
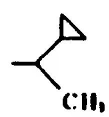
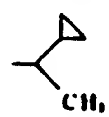
Examples 30 to 43 presented in Table 2 were prepared analogously to the procedure of examples 28 and 29.

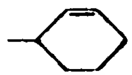
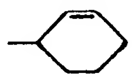
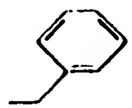
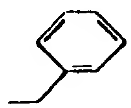
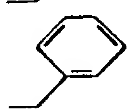
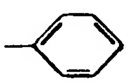
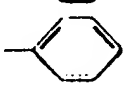
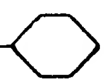
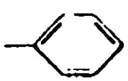
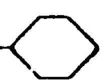
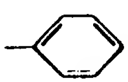
Translator's Note: **Table 2 covers 3 pages of the German text.**

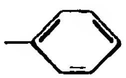
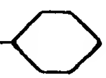
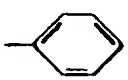
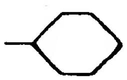
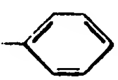
Column headings:

Beispiel Nr.	=	**Example No.**
Summenformel	=	**Empirical formula**
DC	=	**Thin-Layer Chromatography**



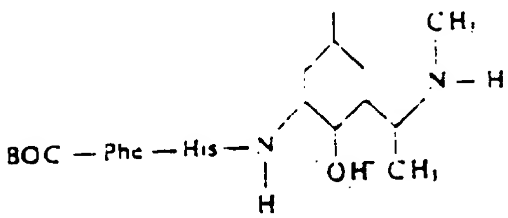
Beispiel Nr	R^1	R^2	R^3	A-B	A-D	E	NMR	Summenformel	FAB-MS M+H [%]	DC
30a, b	iC_4H_9	H	CH_3	BocPro	Phe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	654 [75]	0,24 G
31a	iC_4H_9	H	iC_3H_7	-	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	585 [100]	0,46 H
32	iC_4H_9	H		-	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]S	639 [100]	0,46 I
33	iC_4H_9	H		-	Phe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]S	539 [75]	
34	iC_4H_9	H		-	BocPhe	His		C[illegible]H[illegible]N[illegible]O[illegible]		0,53 G
35	iC_4H_9	H	$-C_6H_{11}$ = Ad	-	BocPhe	His		C[illegible]H[illegible]N[illegible]O[illegible]		0,38 G
36a, a	iC_4H_9	H		-	BocPhe	His		C[illegible]H[illegible]N[illegible]O[illegible]		0,30 I
36ab	iC_4H_9	H		-	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	611 [13]	0,30 I

Beispiel Nr	R^1	R^2	R^3	A-B	A-D	E	NMR	Summenformel	FAB-MS M+H [%]	DC
37 a	iC_4H_9	iC_3H_7	CH_3	BocPro	Phe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	696 [60]	
c	iC_4H_9	iC_3H_7	CH_3	BocPro	Phe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	696 [45]	
38	iC_4H_9		CH_3	–	BocPhe	His		C[illegible]H[illegible]N[illegible]O[illegible]		0,38 G
38 b	iC_4H_9		CH_3	–	BocPhe	His		C[illegible]H[illegible]N[illegible]O[illegible]		0,42 G
39 a	iC_4H_9	CH_3		–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	647 [70]	0,13 E
39 b	iC_4H_9	CH_3		–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	647 [68]	0,46 E
39 c	iC_4H_9	CH_3		–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	647 [70]	0,24 E
40 a	iC_4H_9	iC_3H_7	CH_2– 	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	675 [92]	0,31 F
40 c, d	iC_4H_9	iC_3H_7	CH_2– 	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	675 [78]	0,38 E
41 a	—CH_2— 	iC_3H_7	CH_2– 	–		CH_3–BOM–BocN—His		C[illegible]H[illegible]N[illegible]O[illegible]	702 [100]	0,32 E
42 a	—CH_2— 	iC_3H_7	CH_2– 	–	BocPhe	CH_3–N—His–BOM	x	C[illegible]H[illegible]N[illegible]O[illegible]		0,27 J

Beispiel Nr	R^1	R^2	R^3	A-B	A-D	E	NMR	Summenformel	FAB-MS M+H [%]	DC
42 b	—CH_2—	iC_3H_7	CH_2—	–	BocPhe	CH_3 BOM N — His		C[illegible]H[illegible]N[illegible]O[illegible]		0,34 J
43 a	—CH_2—	iC_3H_7	CH_2—	BocPro	Phe	CH_3 BOM N — His	x	C[illegible]H[illegible]N[illegible]O[illegible]	946 [3,3]	0,42 G
43 b	—CH_2—	iC_3H_7	CH_2—	BocPro	Phe	CH_3 BOM N — His		C[illegible]H[illegible]N[illegible]O[illegible]		0,39 G

Example 44

Peptidylaminoalcohol



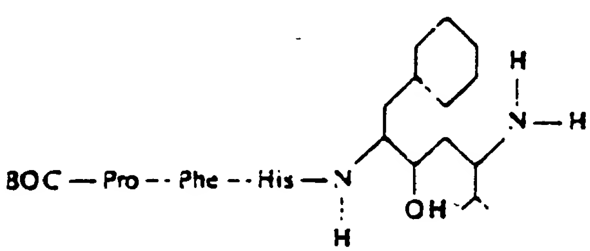
(as)

173 mg (0.3 mmol) of the compound from Example 28 is dissolved in 50 ml methanol. After addition of 378.4 mg (6 mmol) ammonium formate and 259.5 mg 10% Pd/C the mixture is boiled under reflux for 2 hours. As no reaction could be detected quantitatively, the same amounts of ammonium formate and catalyst were added. After a total of 4 hours reaction time the catalyst was suction-filtered off on Celite, the filtrate was evaporated, and the crude material was separated on a preparative HPLC (Vydac).

Mobile phase: 202-40% 0.05% trifluoroacetic acid in CH_3CN, 30 minutes; 10 ml/min. 15.2 mg was obtained.

Example 45

Peptidylaminoalcohol



(at)

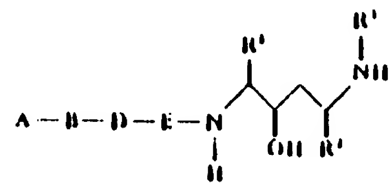
92.8 mg (0.09 mmol) of the compound from Example 43 is dissolved in 10 ml methanol. After addition of 130 mg (2.2 mmol) ammonium formate and 900 mg Pd/C, the mixture is boiled for 2 hours under reflux. The catalyst is removed by suction filtration on silica gel.

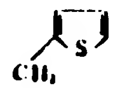
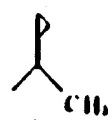
The filtrate is evaporated and dissolved in ethyl acetate. After washing with saturated bicarbonate solution and water, the solution is dried over Na_2SO_4 and evaporated. Yield: 46.9 mg (70.9%).

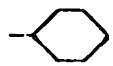
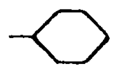
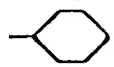
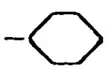
The compounds 46-53, presented in Table 3, were prepared similarly.

Translator's Note: Table 3 takes 2 pages in the original German text.
Column headings:

Beispiel Nr.	=	Example No.
Summenformel	=	Empirical formula
DC	=	Thin-layer Chromatography

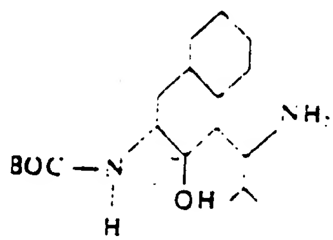


Beispiel Nr	R¹	R²	R³	A-B	A-D	E	NMR	Summenformel	FAB-MS M+H	DC
46	iC_4H_9	H	iC_3H_7		BocPhe	His	x	[illegible]	587 [46]	0,20 I
47	iC_4H_9	H		–	EtocPhe	His	x	[illegible]	613 [40]	0,29 K
48	iC_4H_9	H		–	BocPhe	His	x	[illegible]	615 [100]	
49	iC_4H_9	H	Adamantyl	–	BocPhe	His	x	[illegible]	676 [29]	
50a, a	iC_4H_9	H		–	BocPhe	His	x	[illegible]	613 [68]	
50a, b	iC_4H_9	H		–	BocPhe	His	x	[illegible]	613 [60]	

Beispiel Nr.	R¹	R²	R³	A-B	A-D	E	NMR	Summenformel	FAB-MS M+H [%]	DC
51a, a	iC_4H_9		CH_3	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	641 [98]	
a, b	iC_4H_9		CH_3	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	641 [100]	
b	iC_4H_9		CH_3	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	641 [100]	
52c, a	iC_4H_9	CH_3	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	559 [100]	
c, b	iC_4H_9	CH_3	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	559 [58]	
53a, b	iC_4H_9	iC_3H_7	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	587 [98]	0,29, 0,21
c, d	iC_4H_9	iC_3H_7	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	587 [38]	0,29, 0,21
54a, b	iC_4H_9	iC_3H_7	D—Leu-Z	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	834 [100]	0,301
55a	CH_2— 	iC_3H_7	—CHO	BocPro	Phe	His		C[illegible]H[illegible]N[illegible]O[illegible]	766 [18]	

Example 56

BOC-aminoalcohol



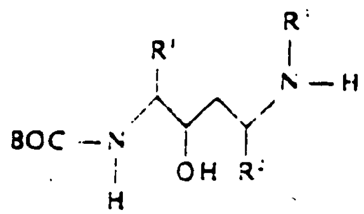
(au)

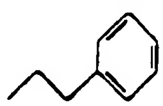
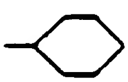
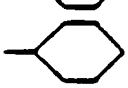
800 mg (1.9 mmol) is produced as in Example 27.
Yield: 431 mg (66.4%).

The compounds 57-61 shown in Table 4 were prepared similarly.

Translator's Note: Table 4 has the same headings:

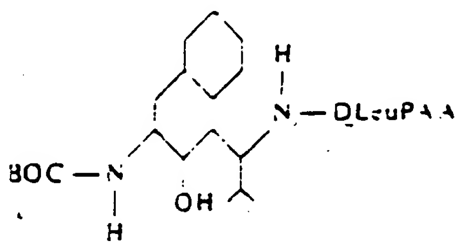
Beispiel No.	**=**	**Example No.**
Summenformel	**=**	**Empirical formula**
DC	**=**	**Thin-layer chromatography**



Beispiel Nr	R^1	R^2	R^3	NMR	Summenformel	FAB-MS M+H [%]	DC
57 a	iC_4H_9	H	CH_3	x	$C_{14}H_{30}N_2O_3$	275 [100] DCI	0.18 I
b	iC_4H_9	H	CH_3		$C_{14}H_{30}N_2O_3$		0.15 I
58 a	iC_4H_9	nC_3H_7	CH_3	x	$C_{17}H_{36}N_2O_3$		0.46 K
b	iC_4H_9	nC_3H_7	CH_3	x	$C_{17}H_{36}N_2O_3$		0.46 K
59 a	iC_4H_9	iC_3H_7	CH_3		$C_{17}H_{36}N_2O_3$		0.05 B
c	iC_4H_9	iC_3H_7	CH_3		$C_{17}H_{36}N_2O_3$		0.05 B
d	iC_4H_9	iC_3H_7	CH_3		$C_{17}H_{36}N_2O_3$		0.05 B
60 a	iC_4H_9		CH_3	x	$C_{22}H_{36}N_2O_3$		0.24 G
c	iC_4H_9		CH_3	x	$C_{22}H_{38}N_2O_3$		0.22 G
61 a, b	CH_2— 	iC_3H_7	CH_3	x	$C_{20}H_{40}N_2O_3$	357 [100]	0.67 K
c, d	CH_2— 	iC_3H_7	CH_3	x	$C_{20}H_{40}N_2O_3$	357 [100]	0.70 K

Example 62a,b

BOC-D-Leucyl-aminoalcohol



(av)

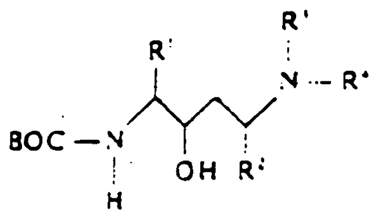
430 mg (1.25 mmol) of the compound from Example 56, 313 mg (1.25 mmol) D-Leucyl-2-pyridylacetic acid, and 0.24 ml (2.50 mmol) of triethylamine are dissolved in 50 ml CH_2Cl_2. 0.61 g (1.375 mmol) 1-benzoxytriazolyloxytris-(dimethylamino)phosphonium hexafluorophosphate us added at 0°C and the mixture is stirred for 16 hours at 20°C. Then the mixture is evaporated, mixed with ethyl acetate and washed three times with saturated bicarbonate solution. The organic phase is dried over Na_2SO_4, dried, evaporated, and chromatographed on silica gel (mobile phase E → G).

Yield: 447.6 mg (63.9%).

The compounds 63-66, presented in Table 5, were prepared similarly.

Translator's Note: Table 5 has the same column headings:

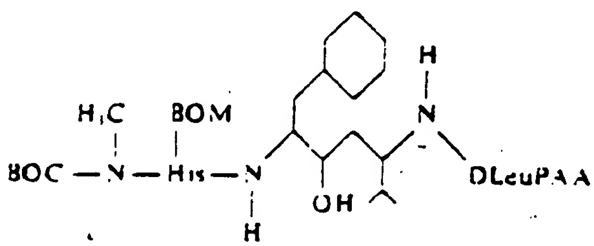
Beispiel Nr.	**=**	**Example No.**
Summenformel	**=**	**Empirical formula**
DC	**=**	**Thin-layer chromatography**



Beispiel Nr.	R^1	R^2	R^3	R^4	NMR	Summenformel	FAB-MS M+H [%]	DC
63 a	iC_4H_9	H	CH_3	D—Leu—Z	x	$C_{28}H_{47}N_3O_6$	522 [17]	0.17 D
b	iC_4H_9	H	CH_3	D—Leu—Z	x	$C_{28}H_{47}N_3O_6$	522 [100]	0.08 D
64 a	iC_4H_9	iC_3H_7	CH_3	D—Leu—Z	x	$C_{31}H_{53}N_3O_6$	564 [100]	0.32 E
c	iC_4H_9	iC_3H_7	CH_3	D—Leu—Z	x	$C_{31}H_{53}N_3O_6$	564 [100]	0.20 E
c	iC_4H_9	iC_3H_7	CH_3	D—Leu—Z	x	$C_{31}H_{53}N_3O_6$	564 [41] DCI	0.39 E
65 a, b	CH_2—⬡	iC_3H_7	CH_3	D—Leu—Z	x	$C_{34}H_{57}N_3O_6$	604 [100] DCI	0.23 E
c, d	CH_2=⬡	iC_3H_7	CH_3	D—Leu—Z	x	$C_{34}H_{57}N_3O_6$	604 [100] DCI	0.35 E
66 b	CH_2—⬡	iC_3H_7	H	D—Leu—Z	x	$C_{33}H_{55}N_3O_6$	590 [22]	0.51 G

Example 67a,b

Peptidyl-D-Leucyl aminoalcohol



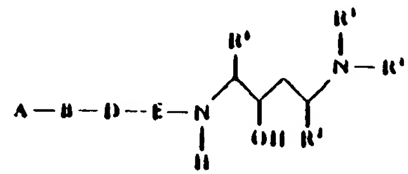
(aw)

447.6 mg (0.78 mmol) BOC-D-Leucyl-aminoalcohol, 62b, is stirred for 30 minutes at 20°C in 5 ml 4N HCl/dioxane. After evaporation and drying in high vacuum,
559 mg of a hydrochloride was obtained. It was dissolved in 30 ml anhydrous tetrahydrofuran along with 426 mg (1.1 mmol) BOC-N-Methyl-His(BOM), 0.12 ml (1.1 mmol) N-methylmorpholine and 336.6 mg (2.2 mmol)hydroxybenzotriazole.
243.3 mg (1.21 mmol) DCC is added at 0°C and stirred for 16 hours at 20°C. Then the solution is filtered from the precipitate. The filtrate is evaporated, and the residue is dissolved in ethyl acetate and washed twice with saturated bicarbonate solution.
After drying over Na_2SO_4 and evaporation, the product is dried in high vacuum.
Yield: 507.8 mg (54.6%)
($C_{47}H_{71}N_7O_7$, DCO, 47 G, M^+H 846 [89%])

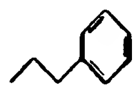
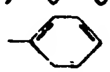
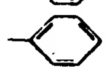
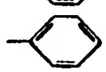
The compounds 68-78 listed in Table 6 were prepared similarly.

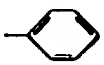
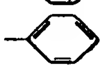
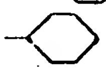
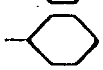
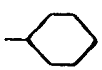
Table 6 covers 2 pages in the German text. Same headings:

Beispiel Nr.	=	**Example No.**
Summenformel	=	**Empirical formula**
DC	=	**Thin-layer chromatography**



I

Beispiel Nr.	R1	R2	R3	R4	A-B	A-D	E	NMR	Summenformel	FAB-MS M+H [%]	DC
68 a	iC[illegible]H[illegible]	H	CH_3	H	BocPro	Phe	His		C[illegible]H[illegible]N[illegible]O[illegible]		
b	iC[illegible]H[illegible]	H	CH_3	H	BocPro	Phe	His		C[illegible]H[illegible]N[illegible]O[illegible]	656 [100]	
69 a	iC[illegible]H[illegible]	nC[illegible]H[illegible]	CH_3	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	601 [100]	
c	iC[illegible]H[illegible]	nC[illegible]H[illegible]	CH_3	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	601 [100]	
70 a	iC[illegible]H[illegible]		CH_3	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	663 [100]	
71 a, b	iC[illegible]H[illegible]		CH_3	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	606 [37]	0.551
b, c	iC[illegible]H[illegible]		CH_3	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	606 [77]	0.391
b	iC[illegible]H[illegible]		CH_3	H	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	606 [42]	0.371
72 a	iC[illegible]H[illegible]	H	CH_3	DLeuZ	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	806 [80]	0.41G
b	iC[illegible]H[illegible]	H	CH_3	DLeuZ	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	806 [71]	0.48G
73 a	iC[illegible]H[illegible]	iC[illegible]H[illegible]	CH_3	DLeuZ	–	BocPhe	His	x	C[illegible]H[illegible]N[illegible]O[illegible]	848 [54]	0.47G

Beispiel Nr	R^1	R^2	R^3	R^4	A-B	A-D	L	NMR	Summenformel	FAB-MS M+H (%)	Rf
74a	iC_4H_9	iC_4H_9	CH_3	DLeuZ	BocPro	Phe	His	x	[illegible]	945 (20)	
c	iC_4H_9	iC_4H_9	CH_3	DLeuZ	BocPro	Phe	His	x	[illegible]	945 (81)	0,56
75b	$-CH_2-$	iC_4H_9	CH_3	DLeuZ	–	BocPhe	His	x	[illegible]	888 (50)	0,55
c	$-CH_2-$	iC_4H_9	CH_3	DLeuZ	–	BocPhe	His	x	[illegible]	888 (64)	
76a, b	CH_2-	iC_4H_9	H	DLeuZ	–	BocPhe	His	x	[illegible]	871 (35)	
b, b	CH_2-	iC_4H_9	H	DLeuZ	–	BocPhe	His	x	[illegible]	871 (11)	
77a, b	CH_2-	iC_4H_9	H	DLeuPAA	–	BocPhe	$CH_3-N-His$		[illegible]	873 (100)	
78a, b	CH_2-	iC_4H_9	H	DLeuPAA	BocPhe	BocPhe	$CH_3-N-His$		[illegible]	970 (6?)	

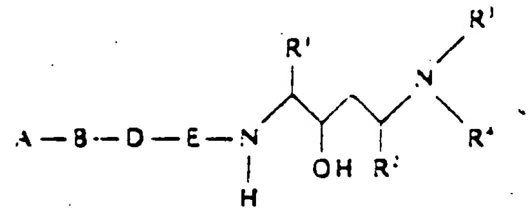
Practical Application

The standard concentration used for the following renin inhibitors is 50 μg/ml. The IC_{50} values were determined at more than 90% inhibition.

Example No.	in vitro 50 μg/ml [%]	IC_{50} [M]
46	70	
49	19	
44	79	
54a,b		9.0×10^{-6}
55		2.9×10^{-7}
72a	90	
76bb		2.2×10^{-6}
78ab		3.8×10^{-8}

Patent Claims

1. Peptides of the general Formula I:

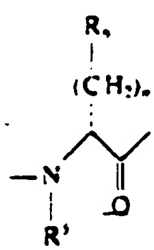


(I)

in which

A is hydrogen or C_1 - C_8 alkyl or C_1 -C_8 alkylcarbonyl or an amine-protecting group,

B is a direct linkage, or a group of the formula



(a)

in which

R^5 is hydrogen, C_1 - C_8 alkyl, phenyl, or an amine-protecting group,

n is the number 0, 1, 2, 3, or 4,

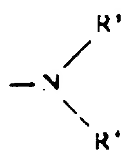
R^6 is hydrogen, C_1 - C_8 alkyl, hydroxymethyl, hydroxyethyl, carboxy, C_1 - C_8 alkylcarbonyl or mercaptomethyl or a group of the formula $-CH_2-NH-R^7$, wherein R^7 is hydrogen, C_1 - C_8 alkyl, phenylsulfonyl, C_1 - C_8 alkylsulfonyl or an amine-protecting group,

or

R^6 is phenyl, naphthyl, guanidinomethyl, methylthiomethyl, halogen, indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, possibly substituted by R^7,

in which R^7 has the meaning given above, or

R^6 is aryl which has up to three identical or different substituents of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1- C_3 alkylbenzyloxy, trifluoromethyl, halogen, hydroxy, nitro, or a group of the formula

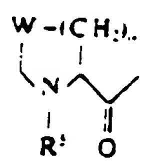


(b)

in which R^8 and R^9 are the same or different and are hydrogen, C_1 - C_8 alkyl, C_1 - C_6 alkylsulfonyl, aryl, arylalkyl, tolylsulfonyl, acetyl, benzoyl or an amine-protecting group,

or

B is a residue



(c)

in which

o is a number 1, 2, 3, or 4,

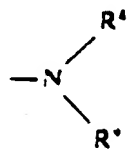
W is methylene, hydroxymethylene, ethylene or sulfur,

R^5 has the meaning given above;

D has the meaning given above for B, and may be the same as B or different,

E has the meaning given above for B, and may be the same as B or different,

R^1 is a straight or branched alkyl chain with 3 to 8 carbon atoms, which can be substituted with halogen, cyano, hydroxy, nitro, cycloalkyl with 3 to 8 carbon atoms, or phenyl, which itself can be substituted by C_1 - C_6 alkyl, nitro, cyano, or halogen, or aryl with 6 to 10 carbon atoms, which can have up to 4 identical or different substituents of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, phenyl, or a group



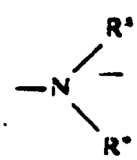
(d)

wherein R^8 and R^9 have the meanings stated above;

R^2 is hydrogen

or

a straight or branched alkyl chain with up to 10 carbon atoms, which may be substituted with halogen, hydroxy, cyano, nitro, or with a group



(e)

in which R^8 and R^9 have the meanings stated above,

or by cycloalkyl with 3 to 8 carbon atoms,

or by phenyl which itself can be substituted by hydroxy, halogen, nitro, or C_1 - C_6 alkyl,

or is saturated or unsaturated cycloalkyl with 3 to 8 carbon atoms,

or is aryl with 6 to 10 carbon atoms, which may be substituted by halogen, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkoxyl, trifluoromethyl, trifluoromethoxy, C_1 - C_6 alkylsulfonyl or C_1 - C_6 alkylcarbonyl;

R^3 and R^4 are identical or different, and are hydrogen or

a straight or branched alkyl chain with up to 10 carbon atoms, which may be substituted by hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, cycloalkyl with up to 8 carbon atoms, heteroaryl or phenyl, which itself may be substituted by nitro, cyano, halogen, C_1 - C_6 alkyl,

or

cycloalkyl with 3 to 8 carbon atoms,

or

adamantyl

or

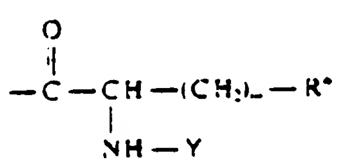
aryl with 6 to 10 carbon atoms, which may be substituted by hydroxy, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, carboxy, C_1 - C_6 alkylcarbonyl, phenyl, phenylsulfonyl, trifluoromethyl or trifluoromethoxy

or

formyl or C_1 - C_6 acyl

or

a group of the formula



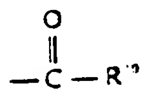
(f)

wherein

m is a number 0, 1, 2, 3 or 4,

R^6 has the meaning stated above,

and Y is an amino-protecting group or a residue of the formula



(g)

wherein

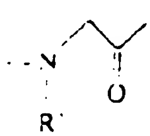
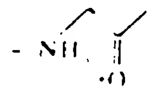
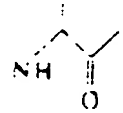
R^{10} is a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by aryl or heteroaryl,

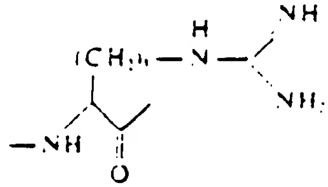
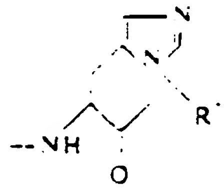
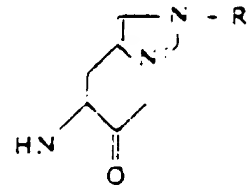
and their physiologically acceptable salts.

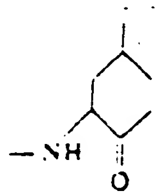
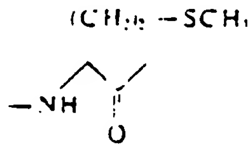
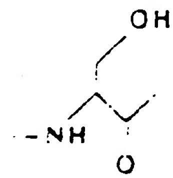
2. Compounds of the general Formula (I) according to Claim 1 in which

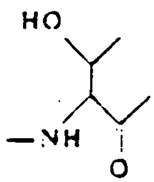
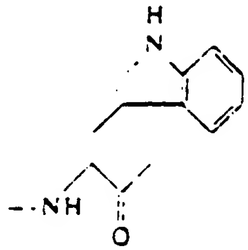
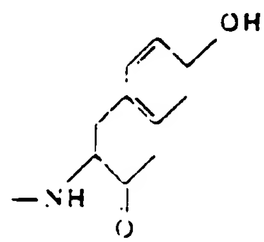
A is hydrogen or C_1 - C_6 alkyl or C_1 - C_6 alkylcarbonyl or an amine-protecting group,

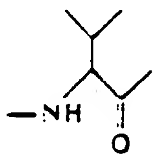
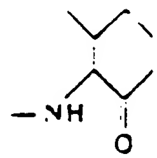
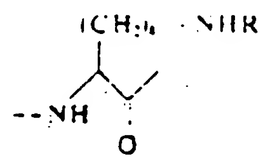
B is a direct linkage or a residue of the formula:

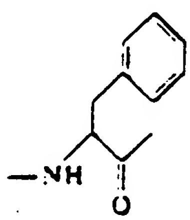
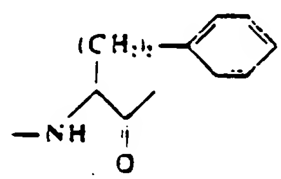
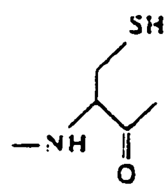




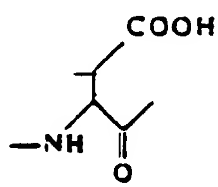
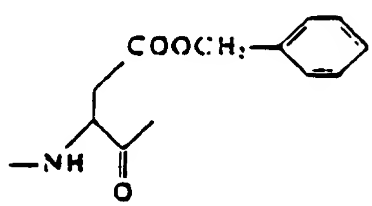
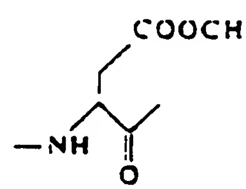




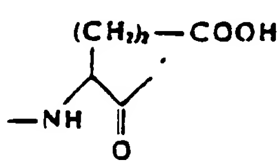
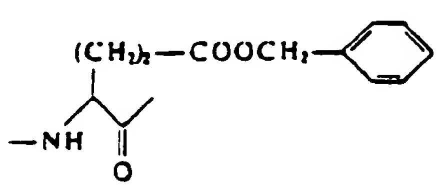




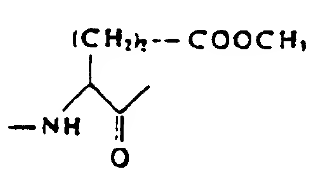
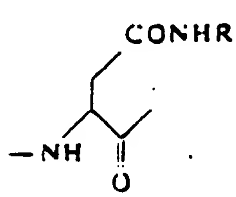




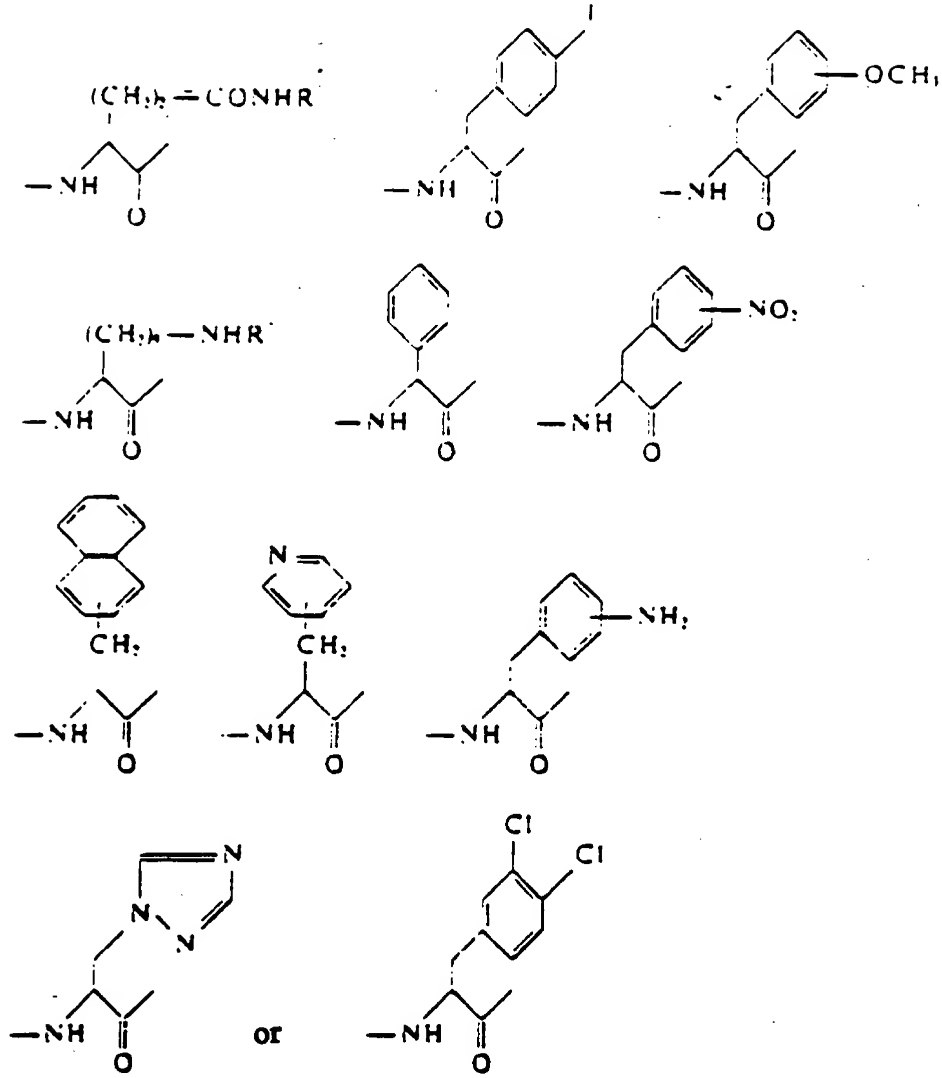




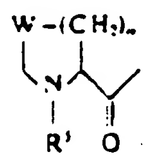





in their D form, L form, or as the DL isomeric mixture, preferably in the L form, wherein

R^7 is hydrogen, C_1 - C_4 alkyl, phenylsulfonyl, C_1 - C_4 alkylsulfonyl or an amine-protecting group,

B is a residue



(i)

wherein

R^5 is hydrogen, C_1 - C_6 alkyl, phenyl, or an amino-protecting group,

o is a number 1, 2, 3, or 4,

W is methylene

in its D form, L form, or DL isomeric mixture, and

D and E are identical or different, and have the same meaning as B, and are the same as B or different from B,

R^1 is a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by halogen, hydroxy, cycloalkyl with 3 to 6 carbon atoms, or phenyl,

or

is phenyl, which has up to 3 substituents of C_1 - C_3 alkyl, C_1 - C_3 alkoxy, hydroxy, nitro, or a group of the formula

(j)

wherein

R^8 and R^9 are identical or different, and are hydrogen, C_1 - C_4 alkyl, phenyl, or an amine-protecting group;

R^2 is hydrogen

or

a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by phenyl, which itself may be substituted by halogen, nitro, or C_1 - C_3 alkyl,

or

saturated or unsaturated cycloalkyl with 3 to 6 carbon atoms

or

phenyl, which may be substituted by halogen, nitro, C_1 - C_3 alkyl, C_1 - C_3 alkoxy or C_1 - C_3 alkoxycarbonyl

and R^3 and R^4 are identical or different, and are hydrogen

or

a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by hydroxy, nitro, thenyl, cycloalkyl with 3 - 6 carbon atoms or phenyl

or

adamantyl

or

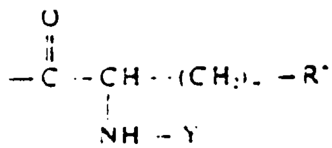
phenyl which may be substituted by hydroxy, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 alkoxcarbonyl

or

formyl

or

a group of the formula



(k)

wherein

m is a number 0, 1, 2, 3, or 4,

R^6 is hydrogen, C_1 - C_6 alkyl, hydroxymethyl, carboxy or a group $-CH_2-NH-R^7$, in which

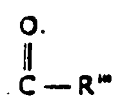
R^7 is hydrogen, C_1 - C_6 alkyl, or an amine-protecting group;

R^6 is guanidinomethyl, methylthiomethyl, halogen, indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, which may be substituted by R^7,

wherein

R_7 has the meaning given above,
or is phenyl, which may be substituted up to twice by halogen, hydroxy or nitro;

Y is an amine-protecting group or a residue of the formula



(l)

wherein

R^{10} is a straight or branched alkyl chain with up to 6 carbon atoms, which may be substituted by phenyl or heteroaryl,

and their physiologically acceptable salts.

3. Compounds of the general Formula (I) according to Claim 1, in which

A is hydrogen or C_1 - C_4 alkyl or C_1 - C_4 alkylcarbonyl or an amine-protecting group, preferably from the series benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, 2-bromoethoxycarbonyl, 2-chloroethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-S-methoxycarbonyl, acetyl, pivaloyl, phthaloyl, 2,2,2-trichloroacetyl, 2,2,2-trifluoroacetyl, benzoyl, 4-nitrobenzoyl, phthalimido, benzyloxymethylene, or tosyl;

B is a direct linkage or glycyl (Gly), alanyl (Ala), arginyl (Arg), histidyl (His), leucyl (Leu), isoleucyl (Ile), seryl (Ser), threonyl (Thr), tryptophyl (Trp), tyrosyl (Tyr), valyl (Val), lysyl (Lys) (possibly with an amino-protecting group or with a methyl substituent on the nitrogen), phenylalanyl (Phe), 2- or 3-nitrophenylalanyl, 2-, 3-, or 4-aminophenylalanyl, naphthylalanine or pyridylalanyl (possibly with an amine-protecting group) in their L or D form,

or

D- or L-prolyl (Pro)

and

D and E are identical or different and have the same meaning as B, and may be the same as B or different;

R_1 is a straight or branched alkyl chain with up to 6 carbon atoms, which may be substituted by cyclopropyl, cyclopentyl or cyclohexyl;

R_2 is hydrogen

or

a straight or branched alkyl chain with up to 5 carbon atoms, possibly substituted by phenyl,

or

cyclohexenyl or cyclohexyl

or

phenyl, which may be substituted by fluorine, chlorine, nitro, methyl or methoxyl;

R^3 and R^4 are identical or different and

are hydrogen

or

a straight or branched alkyl chain with up to 6 carbon atoms, possibly substituted by thenyl, cyclopropyl, cyclopentyl, cyclohexyl or phenyl

or

adamantyl

or

phenyl

or

formyl

or

a group of the formula

$$-\overset{O}{\overset{\|}{C}}-\underset{NH-Y}{\underset{|}{CH}}-(CH_2)_m-R^6 \qquad \text{(m)}$$

wherein

m is a number 0, 1, 2, or 3,

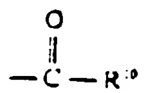
R^6 is hydrogen or C_1 - C_4 alkyl

and

Y is an amine-protecting group

or

a residue of the formula



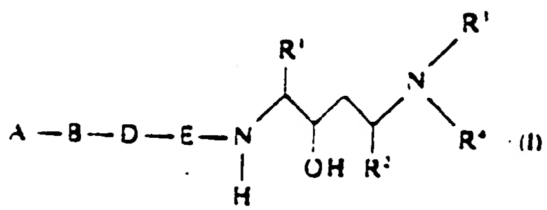
(n)

in which

R^{10} is a straight or branched alkyl chain with up to 4 carbon atoms, possibly substituted by phenyl or pyridyl,

and their physiologically acceptable salts.

4. Process for production of compounds of the general Formula (I)



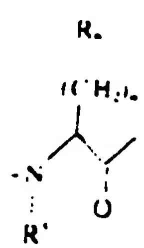
in which

A is hydrogen or C_1 - C_8 alkyl or C_1 - C_8 alkylcarbonyl or an amine-protecting group,

B is a direct linkage

or

a group of the formula



(a)

wherein

R^5 is hydrogen, C_1 - C_8 alkyl, phenyl, or an amine-protecting group,

n is a number 0, 1, 2, 3, or 4,

R^6 is hydrogen, C_1 - C_8 alkyl, hydroxymethyl, hydroxyethyl, carboxy, C_1 - C_8 alkylcarbonyl or mercaptomethyl or a group of the formula

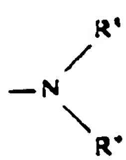
$-CH_2-NH-R^7$,

wherein R^7 is hydrogen, C_1 - C_8 alkyl; phenylsulfonyl, C_1 - C_8 alkylsulfonyl or an amine-protecting group,

or

R^6 is phenyl, naphthyl, guanidinomethyl, methylthiomethyl, halogen, indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, possibly substituted by R^7, in which R^7 has the meaning given above, or

R^7 is aryl which has up to three identical or different substituents of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1- C_3 alkylbenzyloxy, trifluoromethyl, halogen, hydroxy, nitro, or a group of the formula

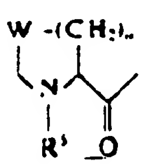


(b)

in which R^8 and R^9 are the same or different and are hydrogen, C_1 - C_8 alkyl, C_1 - C_6 alkylsulfonyl, aryl, arylalkyl, tolylsulfonyl, acetyl, benzoyl or an amine-protecting group,

or

B is a residue



(c)

in which

o is a number 1, 2, 3, or 4,

W is methylene, hydroxymethylene, ethylene or sulfur,

R^5 has the meaning given above;

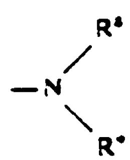
D has the meaning given above for B, and may be the same as B or different,

E has the meaning given above for B, and may be the same as B or different,

R^1 is a straight or branched alkyl chain with 3 to 8 carbon atoms, which can be substituted with halogen, cyano, hydroxy, nitro, cycloalkyl with 3 to 8 carbon atoms, or by phenyl, which itself can be substituted by C_1 - C_6 alkyl, nitro, cyano, or halogen,

or

aryl with 6 to 10 carbon atoms, which can have up to 4 identical or different substituents of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, phenyl, or a group



(d)

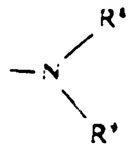
wherein

R^8 and R^9 have the meanings stated above;

R^2 is hydrogen

or

a straight or branched alkyl chain with up to 10 carbon atoms, which may be substituted with halogen, hydroxy, cyano, nitro, or with a group



(e)

in which R^8 and R^9 have the meanings stated above,

or

by cycloalkyl with 3 to 8 carbon atoms,

or by phenyl which itself can be substituted by hydroxy, halogen, nitro, or C_1 - C_6 alkyl,

or is saturated or unsaturated cycloalkyl with 3 to 8 carbon atoms,

or is aryl with 6 to 10 carbon atoms, which may be substituted by halogen, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkoxyl, trifluoromethyl, trifluoromethoxy, C_1 - C_6 alkylsulfonyl or C_1 - C_6 alkylcarbonyl;

R^3 and R^4 are identical or different, and are hydrogen or

a straight or branched alkyl chain with up to 10 carbon atoms, which may be substituted by hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, cycloalkyl with up to 8 carbon atoms, heteroaryl or phenyl, which itself may be substituted by nitro, cyano, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, trifluoromethyl or trifluoromethoxy

or

cycloalkyl with 3 to 8 carbon atoms,

or

adamantyl

or

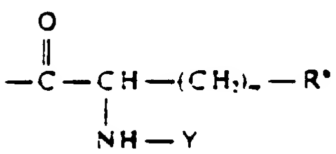
aryl with 6 to 10 carbon atoms, which may be substituted by hydroxy, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, carboxy, C_1 - C_6 alkylcarbonyl, phenyl, phenylsulfonyl, trifluoromethyl or trifluoromethoxy

or

formyl or C_1 - C_6 acyl

or

a group of the formula



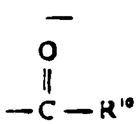
(f)

wherein

m is a number 0, 1, 2, 4 [sic!] or 4,

R^6 has the meaning stated above,

and Y is an amino-protecting group or a residue of the formula



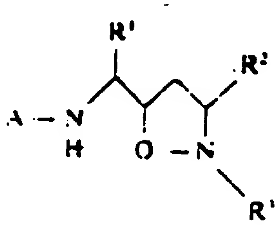
(g)

wherein

R^{10} is a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by aryl or heteroaryl,

and their physiologically acceptable salts,

characterized by the fact that compounds of the general Formula (II)



(p) (II)

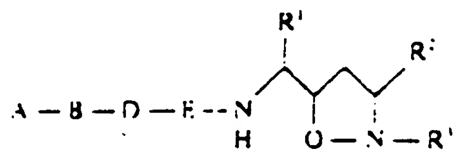
in which A, R^1 and R^2 have the meanings stated above are treated either by

[A] first splitting off the protective group A and then in a second step reacting with compounds of the general Formula (III)

$$A\text{-}B\text{-}D\text{-}E\text{-}OH \qquad (III)$$

in which A, B, D, and E have the meanings stated above,

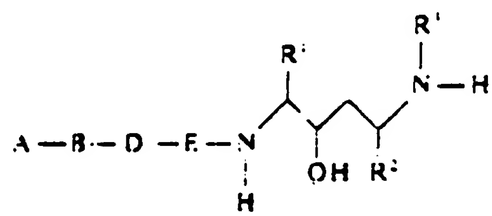
giving compounds of the general Formula (IV)



(q) (IV)

in which A, B, D, E, R^1 and R^2 have the meanings given above,

and then reducing to open the ring by hydrogenolysis, giving compounds of the general Formula Ia



(r) (Ia)

in which A, B, D, E, R^1 and R^2 have the meaning stated above,

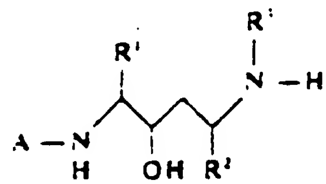
and in the following step reacting with compounds of the general Formula (V)

$$R^4\text{-}OH \qquad (V)$$

in which R^4 has the meaning stated above;

or by

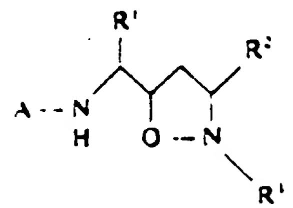
[B] first reducing compounds of the general Formula (II) to aminoalcohols of the general Formula (Ib)



(Ib)

and then reacting with compounds of the general Formula (V), introducing the peptide fragment of the general Formula (III) by the method given above.

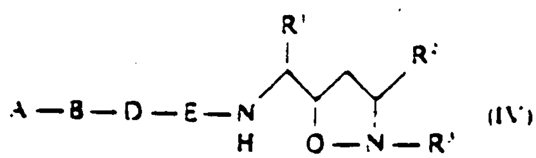
5. Compounds of the general Formula (II)



(II)

in which A, R^1, R^2 and R^3 have the meanings stated in Claim 1.

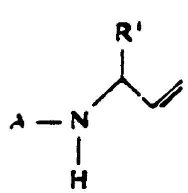
6. Compounds of the general Formula (IV)



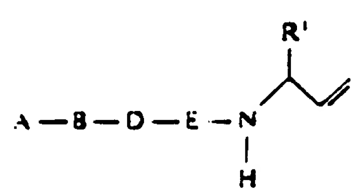
(IV)

in which A, B, D, E, R^1, R^2 and R^3 have the meanings stated in Claim 1.

7. Process for producing compounds of the general Formulas (II) and (IV), characterized by the fact that compounds of the general Formulas (VI) or (VII)

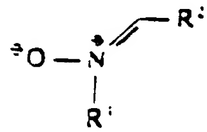


(VI)



(VII)

in which A, B, D, E and R^1 have the meanings stated in Claim 1 are reacted in a cycloaddition reaction with compounds of the general Formula (VIII)



(VIII)

in which R^2 and R^3 have the meanings stated in Claim 1.

8. Compounds of the general Formula (I) according to Claim 1 for application in the treatment of diseases.

9. Medication containing at least one compound of the general Formula (I) according to Claim 1.

10. Process for producing medications, characterized by the fact that compounds of the general Formula (I) according to Claim 1 are converted into suitable dosage forms, using, if necessary, the common auxiliary and carrier materials.

11. Application of compounds of the general Formula (I) according to Claim 1 to produce medications affecting the circulation.